Edwards SAPIEN Transcatheter Heart Valve with the Ascendra Balloon Catheter

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Transapical Approach

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com **or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.**

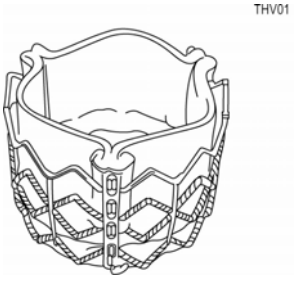
STERILE: The bioprosthesis is supplied sterilized with gluteraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

1.0 Device Description

- Edwards SAPIEN Transcatheter Heart Valve – Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve (bioprosthesis) is comprised of a balloon-expandable, radiopaque, stainless steel (316 L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde

Figure 1. Edwards SAPIEN Transcatheter Heart Valve



Bioprosthesis Diameter	Frame Height (Profile)
23 mm	14.3 mm
26 mm	16.1 mm

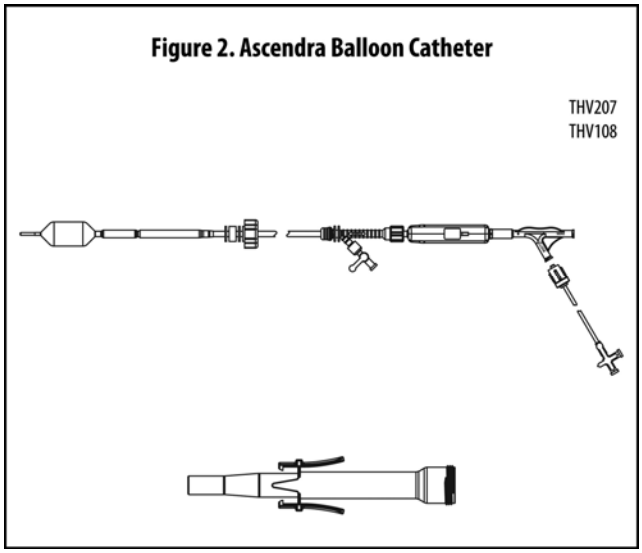
The following table identifies the bioprosthesis size that should be used based on native valve annulus size, as measured by transesophageal echocardiography (TEE).

Native Valve Annulus Size (Tissue Annulus Diameter)	Bioprosthesis Diameter
18-22 mm	23 mm
21-25 mm	26 mm

- Ascendra Balloon Catheter – Model 9100BCL23 for 23 mm valve procedure and 9100BCL26 for 26 mm valve procedure (Figure 2)

The Ascendra Balloon Catheter is used for delivery of the Edwards SAPIEN Transcatheter Heart Valve. The balloon catheter has radiopaque markers for visualization under fluoroscopy and a balloon for deployment of the bioprosthesis. The system also comes with a loader that is used to cover the bioprosthesis during delivery. An extension tubing is supplied for use with the balloon catheter during inflation.

Figure 2. Ascendra Balloon Catheter



2.0 Indications

The Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, is indicated for transapical delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by two cardiac surgeons to be at high risk for surgical aortic valve replacement, not suitable for transfemoral delivery per heart team decision, and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN Transcatheter Heart Valve.

3.0 Contraindications

The bioprosthesis and delivery system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There is an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments.
- The devices are designed, intended, and distributed for single use only. **Do not re-sterilize or reuse the devices.** There are no data to support the sterility, non-pyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the bioprosthesis may lead to paravalvular leak, migration, embolization and/or annular rupture.
- Accelerated deterioration of the bioprosthesis may occur in patients with an altered calcium metabolism.Bioprosthesis must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Bioprosthesis leaflets mishandled or damaged during any part of the procedure will require replacement of the bioprosthesis.
- Caution should be exercised in implanting a bioprosthesis in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the bioprosthesis to ensure proper bioprosthesis positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Do not use the bioprosthesis if the tamper evident seal is broken, the storage solution does not completely cover the bioprosthesis, the temperature indicator has been activated, or the bioprosthesis is damaged, or the expiration date has elapsed.
- Do not mishandle the Ascendra Balloon Catheter or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.
- Patient injury could occur if the delivery system is not un-flexed prior to removal.
- Care should be exercised in patients with hypersensitivities to chromium, nickel, molybdenum, manganese, copper, silicon, and/or polymeric materials
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.
- The safety and efficacy of the transapical procedure has not been evaluated in for only those patient populations where the transfemoral procedure delivery is not suitable.

5.0 Precautions

- Long-term durability has not been established for the bioprosthesis. Regular medical follow-up is advised to evaluate bioprosthesis performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Bioprosthetic valve recipients should be maintained on anticoagulant and antiplatelet therapy (e.g. clopidogrel or ticlopidine [75 mg/day]) for 6 months post procedure and aspirin (75-100 mg/day) for life, except when contraindicated, as determined by their physician.
- The safety of the bioprosthesis implantation has not been established in patients who have:
    - Pre-existing prosthetic heart valve in the aortic position
    - Severe ventricular dysfunction with ejection fraction <20%
    - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
- Safety, effectiveness, and durability have not been established for valve-in-valve procedures.
- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
    - Non-calcified aortic annulus
    - Congenital unicuspid or congenital bicuspid aortic valve
    - Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+)
    - Pre-existing prosthetic heart valve or prosthetic ring in any position
    - Severe mitral annular calcification (MAC), severe (>3+) mitral insufficiency, or Gorelin syndrome
    - Blood dyscrasias defined as: leukopenia (WBC<3000 mm^3), acute anemia (Hb <9 mg%), thrombocytopenia (platelet count <50,000 cells/mm^3), or history of bleeding diathesis or coagulopathy
    - Hypertrophic cardiomyopathy with or without

obstruction (HOCM)

- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated
- Native aortic annulus size <18 mm or >25 mm as measured by echocardiogram
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia

6.0 Potential Adverse Events

Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization for the transapical access procedure, balloon valvuloplasty, and the potential risks of local and/or general anesthesia

- Death
- Stroke/transient ischemic attack clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system injury (defect) which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Femoral AV fistula or pseudoaneurysm
- Reoperation
- Peripheral ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia or to contrast media
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever
- Mechanical failure of delivery system and/or accessories

Additional potential risks specifically associated with the use of the bioprosthesis include, but may not be limited to the following:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Injury at the site of ventricular access that may require repair
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, stent creep, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Injury to the mitral valve
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Non-emergent reoperation

All listed risks may include symptoms associated with the above mentioned medical conditions.

7.0 Directions for Use

7.1 Required Equipment

- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) soft, standard and extra-stiff guidewires
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, and 15% diluted radiopaque contrast medium
- 20 cc or larger luer-lock syringe
- 60 cc or larger luer-lock syringe
- High-pressure 3-way stopcock
- Edwards SAPIEN Transcatheter Heart Valve
- Ascendra Balloon Catheter
- 20 mm balloon valvuloplasty catheter such as Ascendra Balloon Aortic Valvuloplasty Catheter Model 9100BAVC
- Ascendra Introducer Sheath Set Model 9100IS
- Crimper Model 9100CR23 for 23 mm valve procedure and Model 9100CR26 for 26 mm valve procedure
- Inflation device provided by Edwards Lifesciences for this application

7.2 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Bioprosthesis Rinsing Procedure

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g. a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Bioprostheses from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number. Inspect the bioprosthesis for any signs of damage to the frame or tissue.
3	Rinse the bioprosthesis as follows: Place the bioprosthesis in the first bowl of sterile physiological saline. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate (to **gently** swirl the bioprosthesis and holder) back and forth for a minimum of 1 minute. Transfer the bioprosthesis and holder to the second rinsing bowl of physiological saline and gently agitate for at least 1 more minute. Ensure the rinse solution in the first bowl is not used. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls. The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.2.2 Prepare Transapical Procedure Components

Step	Procedure
1	Refer to Ascendra Introducer Sheath Set and Crimper instructions for use on device preparation and handling.
2	Remove the balloon cover from the Ascendra Balloon Catheter
3	Loosen the pusher nut and slide the pusher as far proximal as possible. Rotate the pusher nut to secure the pusher. Slide the loader cap, washers, and seal as far proximal as possible. **CAUTION: Overtightening the pusher nut may result in improper balloon inflation.**
4	Prime and flush the guidewire lumen of the balloon catheter with heparinized saline.
5	Insert an extra stiff guidewire (0.035" [0.89 mm] and ≥ 100 cm long) in the guidewire lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
6	Flush the balloon catheter with heparinized saline through the flush port.
7	Attach extension tubing to balloon inflation port.
8	Prepare a 60 mL or larger luer-lock syringe with diluted contrast medium (15:85 contrast to heparinized saline) and attach it to the balloon extension tubing.
9	Completely fill the inflation device provided by Edwards Lifesciences with diluted contrast medium and attach to the balloon extension tubing.
10	Close stopcock to inflation device. De-air the balloon catheter.
11	Close the stopcock to the syringe. Insert the balloon into the balloon gauge located on the Crimper. Inflate the balloon and verify its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the balloon gauge. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflation solution in the inflation device provided by Edwards Lifesciences until the correct diameter is reached.

Step	Procedure
	The inflation device must remain connected to the balloon catheter throughout the rest of the procedure. **Note:** Correct balloon sizing is critical to successful valve deployment and valve function.
12	Close stopcock to the balloon catheter and remove any remaining diluted contrast medium in the inflation device to the syringe. Lock the inflation device provided by Edwards Lifesciences.
13	Close the stopcock to the syringe and verify the balloon is sized appropriately with the balloon gauge. Remove the syringe.
14	Unlock inflation device provided by Edwards Lifesciences and deflate the balloon while creating a three-wing fold configuration, and ensure no diluted contrast medium is left behind. Lock the inflation device provided by Edwards Lifesciences.

7.2.3 Mount and Crimp the Bioprosthesis on the Balloon Catheter

Step	Procedure
1	Remove the bioprosthesis from the holder and gently place the bioprosthesis into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the balloon catheter with the inflow (fabric cuff end) of the bioprosthesis towards the proximal end of the balloon catheter. Center bioprosthesis between the radiopaque markers.
4	Place the bioprosthesis back in the crimper aperture, and completely crimp until it fits inside the crimp gauge. **CAUTION: The physician must verify correct mounting/orientation of the bioprosthesis prior to its implantation.**
5	Loosen the pusher nut and advance the pusher to align the pusher tip with the proximal end of the crimped bioprosthesis. Rotate the pusher nut to secure the pusher in place. **CAUTION: Overtightening the pusher nut may result in improper balloon inflation.**
6	Flush the loader with sterile heparinized saline and slide the threaded end of the loader over the crimped bioprosthesis.
7	Slide the washers and seal on the balloon catheter shaft distally to the pusher. Insert into loader. Ensure washers and seal are flat against each other within the loader to prevent leakage. Slide loader cap distally over balloon catheter so it sits flat against the washers and seal and rotate the loader cap onto the base of loader. Check that the thread is not exposed. This indicates that the loader cap and seal are fully engaged around the pusher tubing. Do not overtighten the loader cap. **Note:** The loader must fully cover the bioprosthesis.
8	Re-flush the balloon catheter through the flush port and close stopcock to the balloon catheter. **Note:** Keep bioprosthesis hydrated until ready for implantation.
9	Remove guidewire and flush guidewire lumen.

7.3 Valvuloplasty and Bioprosthesis Delivery

Valvuloplasty and bioprosthesis delivery should be performed under general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Valvuloplasty

Refer to Ascendra Balloon Aortic Valvuloplasty Catheter Instructions for Use (IFU) for information on device preparation and handling.

Note: Rapid ventricular pacing should be performed when using the Ascendra Balloon Aortic Valvuloplasty Catheter for valvuloplasty prior to aortic transcatheter valve implantation.

After placement of the balloon at the intended site, begin rapid ventricular pacing. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Bioprosthesis Delivery

Step	Procedure
1	Insert the introducer sheath. Refer to the Ascendra Introducer Sheath Set IFU for additional information on device preparation and handling.
2	Insert loader into the sheath until it locks. Tap lightly on the loader and loosen the loader cap to de-air. Tighten cap until loader is sealed and catheter can move with minimal resistance. Check that the thread is not exposed. This indicates that the loader cap and seal are fully engaged around the pusher tubing. Do not overtighten.
3	Cross the native aortic valve and position the bioprosthesis within the diseased valve.

4	Loosen the pusher nut and retract the pusher, leaving the bioprosthesis in position. Rotate the pusher nut to secure the pusher. Verify that the pusher is completely off of the balloon before it is inflated and the bioprosthesis is deployed. **CAUTION: The pusher must be pulled back for proper balloon inflation and bioprosthesis deployment.**
5	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
6	Verify the correct location of the bioprosthesis with respect to the calcified valve.
7	Begin bioprosthesis deployment: • Unlock the inflation device. • Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the bioprosthesis by inflating the balloon with the entire volume in the inflation device. When the balloon catheter has been completely deflated, turn off the pacemaker. • If deflection was used, straighten the catheter tip. • Retract the balloon catheter into the introducer sheath.
8	Disengage loader from sheath and remove balloon catheter.
9	Remove sheath when the ACT level is appropriate (e.g. reaches < 150 sec). Close apical access site.

8.0 How Supplied

STERILE: The bioprosthesis is supplied sterilized with glutaraldehyde solution. The balloon catheter is supplied sterilized with ethylene oxide gas.

8.1 Storage

The bioprosthesis must be stored between 10 °C-25 °C (50 °F-77 °F).Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the bioprosthesis to extreme temperature.

The Ascendra Balloon Catheter should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3 Tesla.
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33 Ed. 3.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce a temperature rise of less than 1.1 °C above background for a whole body SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T cylindrical whole body MR system, assessed using a GE Signa whole body coil and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.2 W/kg and local background SAR at the site of the implant was 5.6 W/kg. The measured rise above background was 0.7 °C for a whole body SAR of 2 W/kg in a 3.0 T cylindrical bore whole body MR system, assessed using a GE Signa HDx whole body active shield MR scanner with software version 14/LX/MR and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.9 W/kg and local background SAR at the site of the implant was 8.4 W/kg

The image artifact extended as far as 15 mm from the implant for spin echo images and 40 mm for gradient images when scanned in non-clinical testing in a 3.0 T GE Signa HDx MR system. The implant has not been evaluated in MR systems other than 1.5 or 3.0 T.

10.0 Patient Information

A patient registration form is provided with each transcatheter heart valve. After implantation, all requested information should be completed on this form. The serial number may be found on the package and on the identification tag attached to the transcatheter heart valve. The original form should be returned to the Edwards Lifesciences address indicated on the form and provide the temporary identification card to the patient prior to discharge.

11.0 Recovered Clinical Bioprosthesis

The explanted bioprosthesis should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Disposal of Used Devices

Used devices may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies

The Placement of Aortic Transcatheter Valves (PARTNER) trial, a prospective, randomized-controlled, multi-center pivotal trial, evaluated the safety and effectiveness of the Edwards SAPIEN Transcatheter Heart Valve via transfemoral and transapical delivery in a stratified population of high-risk and inoperable patients with severe symptomatic native aortic stenosis. Patients were stratified into two cohorts based on their risk of operability for standard aortic valve replacement surgery – those who were considered high surgical risk were eligible for Cohort A, while inoperable patients were eligible for Cohort B due to coexisting conditions that resulted in the probability of death or irreversible morbidity exceeding 50%.

Study Design – Cohort A

This was a randomized study with the primary objective of ascertaining if TAVR is non-inferior to AVR surgery with respect to 12-month survival outcomes in high-risk surgical patients. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to AVR.

Patients in Cohort A were first evaluated for vascular access to determine whether their peripheral arteries could accommodate the 22 or 24 French sheaths required for the transfemoral TAVR approach to deliver the 23 mm or 26 mm Edwards SAPIEN valve sizes. Those patients who could accommodate these sheaths were then randomized 1:1 between transfemoral TAVR and surgical AVR. Those patients whose arteries could not accommodate these sheaths were randomized 1:1 between transapical TAVR and surgical AVR.

The primary study endpoint was based on a pooled transapical and transfemoral analysis, and was defined as freedom from all-cause mortality at one year for the high-risk cohort. All patients were followed for at least 1 year, and cross-over from the surgical AVR group to the TAVR group was not permitted, except when findings or events during the assigned procedure prevented the planned treatment. Prespecified secondary endpoints included the following: time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within one year for which MACCE definition was comprised of death, MI, stroke, and renal failure as defined by protocol, total hospital days through one year, NYHA functional class at one year, and 6-minute walk test at one year. Additional prespecified efficacy endpoints were measured at 30 days, six months, and one year for the following: functional improvement from baseline as measured per (1) NYHA functional classification, (2) EOA, and (3) 6-minute walk test, freedom from MACCE, improved Quality of Life (QoL), and improved valve function demonstrated by an improvement in EOA.

Study Design – Cohort B

This was a randomized study with the primary objective of ascertaining if TAVR is superior to standard therapy in a control group for inoperable patients with respect to 12-month survival outcomes. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to the standard therapy control group.

Patients in Cohort B were also evaluated for vascular access and those meeting the criteria were randomized 1:1 to either transfemoral delivery of the Edwards SAPIEN valve or to a control group. Patients in the control group were treated with medication and/or balloon valvuloplasty. Patients in Cohort B who did not meet the criteria for vascular access were not eligible for the trial.

Study Results – Cohort A

A total of 699 (657 in the As-Treated [AT] population) high-risk patients with severe aortic stenosis were enrolled at 26 centers (23 in the United States) and assigned to TAVR (344 patients) or AVR (313 patients) with baseline characteristics described in Table 1. Among the TAVR patents, 240 were treated using transfemoral access and 104 were treated using transapical access. Severe aortic stenosis was defined as a mean gradient > 40 mmHg, jet velocity > 4.0 m per sec, or an initial aortic valve area (AVA) of 0.8 cm^2. The primary endpoint for the high-risk cohort was freedom from all-cause mortality at one year. Clinical outcomes of TAVR (transfemoral and transapical) as compared to AVR are summarized in Tables 5, 6, and 7. At day 365, the Kaplan-Meier estimate of all-cause death was 23.7% in the TAVR group, as compared to 25.2% in the AVR group. The estimated difference between these treatment groups is -1.5% with a one-sided lower 95% confidence interval of -4.0%, which is greater than the pre-specified margin of -7.5%. The non-inferiority p-value for this difference is 0.0037, indicating that TAVR is non-inferior to AVR with respect to all-cause death [Figure 3]. Pre-specified secondary endpoints included valve performance [Figures 6 and 7] and NYHA functional class [Figure 8]. When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR was more likely than AVR to reduce cardiac symptoms (New York Heart Association class ≤ II) (P<0.0030). At 1 year, both TAVR and AVR improved cardiac symptoms with no evidence of treatment differences. The majority of strokes were reported at ≤ 30 days; the rate was 4.4% in the TAVR arm and 2.6% in the AVR arm (P=0.2064). At one year, the rate of stroke was 5.8% in the TAVR arm and 3.0% in the AVR arm (P=0.0887). Hemorrhagic/vascular events occurred in 24.5% of TAVR patients as compared to 27.8% of AVR patients between 0 and 30 days (P=0.3332). Between 0 days and one year, hemorrhagic/vascular events occurred in 26.8% of TAVR patients as compared to 28.6% of AVR patients (P=0.6248). Bleeding events occurred in 10.2% of TAVR patients vs. 28.4% of AVR patients (P<0.0001) between 0 and 30 days and in 10.2% of TAVR patients vs. 28.4% of AVR patients between 0 and 365 days (P<0.0001). New-onset atrial fibrillation was seen in 8.7% of TAVR patients as compared to 18.2% of AVR patients (P=0.0005). Aortic valve gradients and areas improved significantly after TAVR and AVR at 30 days and 1 year. There were small differences in aortic valve gradients and areas favoring TAVR (at 1 year, mean gradient 10.2 vs. 11.4 mm Hg; P=0.0131 and valve area 1.59 vs. 1.44 cm^2; P=0.0027). Moderate or severe para-valvular regurgitation was more

frequent after TAVR than AVR (at 30-days, 11.7% vs. 0.9%, respectively, with P<0.0001; at 1-year, 6.5% vs. 1.9%, respectively, with P<0.0469).

In patients with severe aortic stenosis who are at high-risk for operation, TAVR and AVR had similar survival after 1 year and similar improvement in cardiac symptoms. TAVR patients experienced a higher incidence of strokes and major vascular events. AVR patients experienced a higher incidence of bleeding. With respect to the transfemoral approach in both the ITT and AT populations, all cause mortality in the TAVR arm was non-inferior to all cause mortality in the AVR arm at 1 year. With respect to the transapical approach in both the ITT and AT populations, all cause mortality was not shown to be non-inferior to all cause mortality in the AVR arm at 1 year. The study was not powered for this analysis.In conclusion, when used in the high surgical risk population the benefits and risks associated with TAVR are not inferior to the risks and benefits associated with surgical AVR.

Study Results – Cohort B

A total of 358 patients (ITT population) with severe aortic stenosis were enrolled and underwent 1:1 randomization at 22 centers (18 in the United States) with baseline characteristics described in Table 2. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mmHg or more, or a peak aortic-jet velocity of 4.0 m per second or more. The primary end point was the rate of death from any cause over the duration of the trial. At 1 year, the rate of death from any cause (Kaplan-Meier analysis) was 30.7% with TAVR, as compared with 50.7% in the group not receiving the valve (hazard ratio with TAVR, 0.51; 95% confidence interval [CI], 0.39 to 0.68; P < 0.0001) (Figure 9). A total of 141 of the 179 (78.8%) patients in the control group underwent balloon aortic valvuloplasty (BAV). In addition, 11 patients (6.1%) underwent aortic valve replacement. 5 patients (2.8%) received an LV-descending aortic conduit, and 4 patients (2.2%) received a THV outside the US. The co-primary composite end point was time of death from any cause or the time to the first occurrence of repeat hospitalization. The rate of the composite end point of death from any cause or repeat hospitalization was 43.6% with TAVR as compared with 71.6% in the control group (hazard ratio, 0.45; 95% CI, 0.35 to 0.59; P < 0.0001) (Figure 10). Prespecified secondary end points included the rate of death from cardiovascular causes (Figure 11), NYHA functional class (Figure 14), valve performance (Figures 12 and 13), and the distance covered during a 6-minute walk test. Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVR than among those in the control group (23.9% vs. 60.8%, P < 0.001). When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR, as compared with the control, was associated with a higher incidence of strokes (7.3% vs. 1.7%, P = 0.02) and major vascular complications (16.8% vs. 1.1%, P < 0.0001). The time from index procedure to stroke in the TAVR group was as follows: 1 stroke at 12 days before the index procedure but after randomization, 4 strokes on the day of the index procedure, 2 strokes on the first post-operative day and 2 on the second post-operative day, and one stroke each on days 3, 5, 10, 23, 39, 51, 75, 120, 136, and 151. At 1 year, the rate of hemorrhagic vascular complication was 34.3% in the TAVR group, as compared to 17.7% in the control group. At 1 year, the rate of bleeding events was 17.3% in the TAVR group, as compared to 2.2% in the control group. Additionally, at 1 year, the rate of endocarditis was 1.4% in the TAVR group, as compared to 0.8% in the control group. Mean index hospital stay was 8.5 days for the TAVR group, as compared to 7.6 days for the control group. Mean days alive out of hospital was 273.8 days for the TAVR group and 210.2 days for the control group. At 1 year, the rate of aortic regurgitation for the TAVR group was as follows: 2% of patients at 4+, 13% of patients at 3+, 50% of patients at 2+, 20% of patients at 1+, and 11% of patients with no regurgitation. In comparison, the rate of aortic regurgitation of the control group was as follows: 17% of patients at 3+, 39% of patients at 2+, 37% of patients at 1+, and 7% of patients with no regurgitation.

Procedure data for the TAVR group is summarized in Table 4. Clinical outcomes of TAVR as compared with the control are summarized in Table 8. In the two years after TAVR, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram.

Additional data for the inoperable patient population in Cohort B has been collected, reviewed, and adjudicated; results are summarized in Table 8.

In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, as compared with the control, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of stroke and major vascular events.

Non-Randomized Continued Access (NRCA) – Cohort A

Once study enrollment in the randomized protocol for Cohort A had been completed, 1521 additional patients were treated and followed in a non-randomized continued access cohort. Non-randomized continued access allowed eligible subjects to be treated with TAVR without randomization.

The non-randomized as treated cohort comprises 1521 patients and consists of 822 NRCA transapical patients and 699 NRCA transfemoral patients. In order to compare the randomized cohort population to the non-randomized population, pertinent demographic and baseline characteristics were compared post hoc. Compared to the randomized TAVR patients, the age of NRCA patients was slightly higher and more NRCA patients were female. In addition, NRCA patients had a higher incidence of CAD, prior PCI, and prior BAV and lower incidence of pulmonary hypertension and frailty compared to the randomized TAVR patients. Comparison of the key demographic and baseline characteristics of the high risk randomized TAVR patients vs. the NRCA patients may be found in Table 9. Inclusion criteria for the non-randomized cohort were the same as inclusion criteria for the randomized cohort.

Clinical outcomes of the NRCA population as compared to the randomized population may be found in Table 11. The Kaplan-Meier estimate, at 30 days, of all-cause mortality in the pooled NRCA group was 5.9%; the Kaplan-Meier estimate, at Day 365, of all-cause mortality in the pooled NRCA group was 21.6%. The respective Transapical Kaplan-Meier estimates at 30 days and 365 days were 8.2% and 23.6%; the respective Transfemoral Kaplan-Meier estimates at 30 days and 365 days were 3.2% and 19.4 %.

The Kaplan-Meier rate of stroke in the NRCA Transapical group at 30 days was 2.0%, whereas the Kaplan-Meier rate of stroke in the NRCA Transfemoral group at 30 days was 4.4%. At day 365, the Kaplan-Meier rate of stroke was 3.7% and 5.7% for Transapical and Transfemoral, respectively.

Death and stroke data from 1521 pooled non-randomized continued access patients are available [Table 11]. These outcomes are better than as the results obtained in the randomized TAVR cohort at one year.

Table 1: COHORT A - Baseline Characteristics of the Patients and Echocardiographic Findings* (AT Population)							
	Transapical Approach		Transfemoral Approach		Pooled Approaches		
	AVR	TAVR	AVR	TAVR	AVR	TAVR	P Value
Characteristic	(N = 92)	(N = 104)	(N = 221)	(N = 240)	(N = 313)	(N = 344)	
Age — yr	83.4 ± 5.5	82.9 ± 7.0	84.8 ± 6.6	83.9 ± 6.8	84.4 ± 6.3	83.6 ± 6.8	0.12
Male sex — no. (%)	55 (59.8)	53 (51.0)	124 (56.1)	145 (60.4)	179 (57.2)	198 (57.6)	0.94
STS score†	12.01 ± 3.5	11.7 ± 3.6	11.5 ± 3.3	11.9 ± 3.2	11.7 ± 3.4	11.8 ± 3.3	0.65
NYHA class — no. (%):							
II	4/92 (4.3)	8/104 (7.7)	12/221 (5.4)	12/240 (5.0)	16/313 (5.1)	20/344 (5.8)	0.73
III or IV	88/92 (95.7)	96/104 (92.3)	209/221 (94.6)	228/240 (95.0)	297/313 (94.9)	324/344 (94.2)	>0.999
Coronary artery disease — no. (%)	76/92 (82.6)	77/104 (74.0)	165/221 (74.7)	181/240 (75.4)	241/313 (77.0)	258/344 (75.0)	0.58
Previous myocardial infarction — no./total no. (%)	34/92 (37.0)	28/104 (26.9)	56/218 (25.7)	64/239 (26.8)	90/310 (29.0)	92/343 (26.8)	0.54
Previous intervention — no./total no. (%)							
CABG	51/92 (55.4)	51/104 (49.0)	88/221 (39.8)	95/240 (39.6)	139/313 (44.4)	146/344 (42.4)	0.64
PCI	39/91 (42.9)	33/104 (31.7)	62/221 (28.1)	82/238 (34.5)	101/312 (32.4)	115/342 (33.6)	0.74
Balloon aortic valvuloplasty	10/92(10.9)	13/104(12.5)	22/221(10.0)	33/240(13.8)	32/313(10.2)	46/344(13.4)	0.2287
Cerebral vascular disease — no./total no. (%)	26/86 (30.2)	40/96 (41.7)	53/206 (25.7)	56/227 (24.7)	79/292 (27.1)	96/323 (29.7)	0.48
Peripheral vascular disease — no./total no. (%)	56/90 (62.2)	65/103 (63.1)	76/217 (35.0)	83/238 (34.9)	132/307 (43.0)	148/341 (43.4)	0.94
COPD — no./total no. (%):							
Any	41/92 (44.6)	46/104 (44.2)	97/221 (43.9)	104/240 (43.3)	138/313 (44.1)	150/344 (43.6)	0.94
Oxygen-dependent	7/92 (7.6)	11/104 (10.6)	16/221 (7.2)	21/240 (8.8)	23/313 (7.3)	32/344 (9.3)	0.90
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	9/92 (9.8)	7/103 (6.8)	11/221(5.0)	30/237 (12.7)	20/313 (6.4)	37/340 (10.9)	0.05
Atrial fibrillation — no./total no. (%)	17/33 (51.5)	31/58 (53.4)	51/121 (42.1)	49/138 (35.5)	68/154 (44.2)	80/196 (40.8)	0.59
Permanent pacemaker — no./total no. (%)	17/92 (18.5)	21/104 (20.2)	53/221 (24.0)	48/240 (20.0)	70/313 (22.4)	69/344 (20.1)	0.50
Pulmonary hypertension — no./total no. (%)	38/92 (41.3)	55/104 (52.9)	112/221 (50.7)	117/240 (48.8)	150/313 (47.9)	172/344 (50.0)	0.07
Extensively calcified aorta — no. (%)	1/92 (1.1)	2/104 (1.9)	1/221 (0.5)	0/240 (0.0)	2/313 (0.6)	2/344 (0.6)	>0.999
Deleterious effects of chest-wall irradiation — no. (%)	0/92 (0.0)	2/104 (1.9)	2/221 (0.9)	1/240 (0.4)	2/313 (0.6)	3/344 (0.9)	>0.999
Chest-wall deformity — no. (%)	1/92 (1.1)	0/104 (0.0)	0/221 (0.0)	0/240 (0.0)	1/313 (0.3)	0/344 (0.0)	0.48
Liver disease — no./total no. (%)	0/92 (0.0)	2/104 (1.9)	9/221 (4.1)	6/240 (2.5)	9/313 (2.9)	8/344 (2.3)	0.81

Echocardiographic findings							
Aortic-valve area — cm^2 (n, mean)	88, 0.7 ± 0.2	95, 0.7 ± 0.2	207, 0.6 ± 0.2	223, 0.7 ± 0.2	295, 0.6 ± 0.2	318 ,0.7 ± 0.2	0.28
Mean aortic-valve gradient — mmHg (n, mean)	90, 40.5 ± 12.9	97, 41.7 ± 13.9	210, 44.6 ± 14.8	229, 43.0 ± 14.8	300, 43.4 ± 14.3	326, 42.6 ± 14.5	0.49
Mean LVEF — (n, mean)	89, 53.5 ± 10.9	98, 53.6 ± 12.2	211, 53.3 ± 13.3	232, 52.2 ± 14.0	300, 53.3 ± 12.6	330, 52.6 ± 13.5	0.48
Moderate or severe mitral regurgitation — no./total no. (%)¶	19/89 (21.3)	19/99 (19.2)	44/208 (21.2)	46/230 (20.0)	63/297 (21.2)	65/329 (19.8)	0.69

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 2: COHORT B - Baseline Characteristics of the Patients and Echocardiographic Findings* (ITT Population)			
	TAVR	Control Group	P Value
Characteristic	(N = 179)	(N = 179)	
Age — yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex — no. (%)	82 (45.8)	84 (46.9)	0.92
STS score†	11.2 ± 5.8	11.9 ± 4.8	0.14
NYHA class — no. (%):			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease — no. (%)	121 (67.6)	133 (74.3)	0.20
Previous myocardial infarction — no./total no. (%)	33/177 (18.6)	47/179 (26.3)	0.10
Previous intervention — no./total no. (%)			
CABG	58/179 (32.4)	73/179 (40.8)	0.12
PCI	47/179 (26.3)	39/179 (21.8)	0.39
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease — no./total no. (%)	48/175 (27.4)	46/171 (26.9)	1.00
Peripheral vascular disease — no./total no. (%)	55/178 (30.9)	45/179 (25.1)	0.24
COPD — no. (%):			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	8/179 (4.5)	16/178 (9.0)	0.10
Atrial fibrillation — no./total no. (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker — no./total no. (%)	35/179 (19.6)	31/179 (17.3)	0.68
Pulmonary hypertension — no./total no. (%)	50/118 (42.4)	53/121 (43.8)	0.90
Extensively calcified aorta — no. (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation — no. (%)	16 (8.9)	15 (8.4)	1.00
Chest-wall deformity — no. (%)	15 (8.4)	9 (5.0)	0.29
Liver disease — no./total no. (%)	6/177 (3.4)	6/178 (3.4)	1.00
Echocardiographic findings			
Aortic-valve area — cm2	0.6 ± 0.2	0.6 ± 0.2	0.97
Mean aortic-valve gradient — mmHg	44.5 ± 15.7	43.0 ± 15.3	0.39
Mean LVEF — %	53.9 ± 13.1	51.1 ± 14.3	0.06
Moderate or severe mitral regurgitation — no./total no. (%)¶	38/171 (22.2)	38/165 (23.0)	0.90

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 3: COHORT A - Procedure Data (AT Population)			
	TA TAVR	**TF TAVR**	**Pooled AVR**
Variable	**Mean of % of patients (min-max)**		
Total time of procedure (min)	225 (93 - 595)	246 (84 - 624)	333 (70 - 750)
Skin to skin time (min)	114	142	230 (169 - 295)
Fluoroscopy time (min)	35	30	N/A
Volume of contrast (ml)	104	148	N/A
Use of CPB	8.8%	2.1%	100%
Use of general anesthesia	100%	100%	100%
# of devices used			
0	2.9%	4.6%	N/A
1	89.2%	90.8%	100%
2	6.9%	4.2%	N/A
3	1.0%	0.4%	N/A
Valve in valve procedure	1.0%	0.4%	N/A
Emergent operation due to device or procedure	1.0%	1.3%	3.8%
Valve Size			
19 mm	N/A	N/A	11.9%
21 mm	N/A	N/A	39.7%
22 mm	N/A	N/A	0.3%
23 mm	51.5%	46.8%	34.9%
25 mm	N/A	N/A	11.9%
26 mm	48.5%	53.3%	N/A
27 mm	N/A	N/A	1.0%
29 mm	N/A	N/A	0.3%
Adverse event during procedure	19.6%	21.3%	14.7%
Device malfunction	2.0%	1.3%	N/A
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	84.5%	80.4%	N/A
Procedure Success (Device success, no MACCE < 30d)	75.3%	76.0%	N/A

Table 4: COHORT B - TAVR Procedure Data	
Variable	**Mean or % of patients (min – max)**
Total time of procedure (min)	262 (139-616)
Skin to skin time (min)	150 (34 – 553)
Fluoroscopy time (min)	29 (10-68)
Volume of contrast (ml)	132 (10-450)
Use of CPB	1.1%
Use of general anesthesia	100%
# of devices used 0 1 2 3	 4.6% 89.1% 5.7% 0.6%
Valve in Valve procedure	2.3%
Emergent operation due to device or procedure	1.1%
Valve Size 23 mm 26 mm	 56.6% 43.4%
Adverse event during procedure	39.4%
Device malfunction	3.4%
Device Success (deployment, AVA >0.9, AI<3+, 1 valve)	78.2%
Procedure Success (Device success, no MACCE <30d)	71.8%

Table 5: COHORT A - Clinical Outcomes of the Pooled TAVR and Pooled AVR Groups up to 2 Years (AT Population)

	30 Days				31 Days - 1 Year				1 Year - 2 Years			
Outcome	Pooled TAVR N=344	KM Event rate TAVR*	Pooled AVR N=313	KM Event rate AVR	Pooled TAVR N=344	KM Event rate TAVR*	Pooled AVR N=313	KM Event rate AVR	Pooled TAVR N=344	KM Event rate TAVR*	Pooled AVR N=313	KM Event rate AVR
Death	18	5.2%	25	8.0%	63	23.7%	53	25.2%	33	33.9%	21	32.7%
Death from cardiovascular cause[a]	14	4.1%	9	2.9%	30	13.6%	24	11.5%	20	20.8%	16	18.5%
Repeat hospitalization[b]	18	5.4%	18	6.1%	40	17.3%	29	16.6%	15	23.8%	9	20.8%
Death from any cause or repeat hospitalization[b]	35	10.2%	43	13.8%	86	33.9%	74	35.5%	48	46.2%	33	44.4%
TIA[d]	3	0.9%	1	0.3%	5	2.7%	3	1.5%	2	3.6%	2	2.7%
All Stroke[c]	15	4.4%	8	2.6%	4	5.8%	1	3.0%	4	7.5%	3	4.4%
Myocardial Infarction[g]												
All	0	0.0%	1	0.3%	0	0.0%	0	0.3%	2	0.0%	0	1.3%
Peri-procedural	0	0.0%	1	0.3%	0	0.0%	0	0.3%	0	0.0%	0	0.3%
Hemorrhagic Vascular Complication[f]	84	24.5%	87	27.8%	10	26.8%	3	28.6%	3	28.0%	2	29.4%
Major Vascular Complication[i]	38	11.1%	12	3.8%	0	11.1%	0	3.8%	1	11.4%	0	3.8%
Renal Failure[h]	13	3.8%	14	4.6%	4	5.2%	5	6.5%	2	6.0%	0	6.5%
Renal Insufficiency	19	5.6%	18	5.8%	3	6.6%	7	7.8%	4	8.1%	1	8.3%
Bleeding Event[e]	35	10.2%	89	28.4%	0	10.2%	0	28.4%	0	10.2%	0	28.4%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	7	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	1	0.3%	3	1.0%	2	1.1%	1	1.5%	0	1.1%
New Atrial Fibrillation[j]	30	N/A	57	N/A	14	N/A	3	N/A	N/A	N/A	N/A	N/A
New pacemaker	16	4.7%	14	4.6%	4	6.1%	2	5.3%	2	6.9%	3	6.8%

*Kaplan-Meier event rates are reported at 30 days,one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 6: COHORT A - Clinical Outcomes in the Transfemoral Group up to 2 Years (AT Population)

	30 Days				31 Days - 1 Year				1 Year – 2 Years			
Outcome	TF TAVR N=240	KM Event rate TAVR*	AVR N=221	KM Event rate AVR	TF TAVR N=240	KM Event rate TAVR*	AVR N=221	KM Event rate AVR	TF TAVR N=240	KM Event rate TAVR*	AVR N=221	KM Event rate AVR
Death	9	3.7%	18	8.2%	42	21.4%	37	25.2%	21	30.7%	13	31.6%
Death from cardiovascular cause[a]	8	3.3%	7	3.2%	19	12.0%	17	11.8%	14	19.0%	9	17.3%
Repeat hospitalization[b]	13	5.5%	12	5.8%	29	17.6%	22	17.3%	8	22.4%	4	19.8%
Death from any cause or repeat hospitalization[b]	21	8.7%	30	13.6%	59	31.8%	52	35.3%	31	42.2%	18	42.2%
TIA[d]	3	1.3%	0	0.0%	2	2.3%	1	0.6%	1	2.8%	1	1.4%
All Stroke[c]	8	3.3%	3	1.4%	1	3.8%	0	1.4%	2	5.0%	1	2.0%
Myocardial Infarction[g]												
All	0	0.0%	1	0.5%	0	0.0%	0	0.5%	1	0.0%	0	1.1%
Peri-procedural	0	0.0%	1	0.5%	0	0.0%	0	0.5%	0	0.0%	0	0.5%
Hemorrhagic Vascular Complication[f]	69	28.8%	61	27.6%	5	30.2%	2	28.7%	1	30.7%	2	29.8%
Major Vascular Complication[i]	34	14.2%	7	3.2%	0	14.2%	0	3.2%	1	14.7%	0	3.2%
Renal Failure[h]	8	3.4%	7	3.2%	3	4.7%	4	5.5%	2	5.8%	0	5.5%
Renal Insufficiency	7	2.9%	13	6.0%	2	3.9%	6	8.2%	4	5.9%	0	8.2%
Bleeding Event[e]	27	11.3%	63	28.5%	0	11.3%	0	28.5%	0	11.3%	0	28.5%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	4	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	0	0.0%	2	1.0%	2	1.1%	1	1.6%	0	1.1%
New Atrial Fibrillation[j]	19	N/A	42	N/A	11	N/A	2	N/A	N/A	N/A	N/A	N/A
New pacemaker	11	4.6%	9	4.2%	3	6.0%	0	4.2%	2	7.2%	3	6.2%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR). c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular

surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 7: COHORT A - Clinical Outcomes in the Transapical Group up to 2 Years (AT Population)

	30 Days				31 Days - 1 Year				1 Year – 2 Years			
Outcome	TA TAVR N=104	KM Event rate TAVR*	AVR N=92	KM Event rate AVR	TA TAVR N=104	KM Event rate TAVR8	AVR n=92	KM Event rate AVR	TA TAVR N=104	KM Event rate TAVR*	AVR N=92	KM Event rate AVR
Death	9	8.7%	7	7.6%	21	29.1%	16	25.3%	12	41.3%	8	35.5%
Death from cardiovascular cause[a]	6	5.8%	2	2.2%	11	17.4%	7	10.8%	6	25.2%	7	21.6%
Repeat hospitalization[b]	5	5.1%	6	6.8%	11	16.7%	7	14.9%	7	27.4%	5	23.3%
Death from any cause or repeat hospitalization[b]	14	13.5%	13	14.1%	27	38.7%	22	36.3%	17	55.3%	15	49.6%
TIAd[d]	0	0.0%	1	1.1%	3	3.7%	2	3.9%	1	5.8%	1	5.6%
All Stroke[c]	7	7.0%	5	5.5%	3	10.8%	1	7.0%	2	13.8%	2	10.0%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.0%	0	15.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Hemorrhagic Vascular Complication[f]	15	14.5%	26	28.3%	5	19.2%	1	28.3%	2	22.0%	0	28.3%
Major Vascular Complication[i]	4	3.9%	5	5.4%	0	3.9%	0	5.4%	0	3.9%	0	5.4%
Renal Failure[h]	5	5.0%	7	7.7%	1	6.2%	1	8.9%	0	6.2%	0	8.9%
Renal Insufficiency	12	11.9%	5	5.5%	1	13.1%	1	6.9%	0	13.1%	1	8.4%
Bleeding Event[e]	8	7.7%	26	28.3%	0	7.7%	0	28.3%	0	7.7%	0	28.3%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	3	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Endocarditis	0	0.0%	1	1.1%	1	1.2%	0	1.1%	0	1.2%	0	1.1%
New Atrial Fibrillation[j]	11	N/A	15	N/A	3	N/A	1	N/A				
New pacemaker	5	5.0%	5	5.6%	1	6.2%	2	8.1%	0	6.2%	0	8.1%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 8: Cohort B - Clinical Outcomes up to 2 Years (ITT Population)

	30 Days				31 Days - 1 Year				1 Year - 2 Years			
Outcome	TAVR N=179	KM Event rate*	Control Group N=179	KM Event rate	TAVR N=179	KM Event rate*	Control Group N=179	KM Event rate	TAVR N=179	KM Event rate*	Control Group N=179	KM Event rate
Death from any cause	9	5.0%	5	2.8%	46	30.7%	84	50.7%	22	43.3%	28	68.0%
Death from cardiovascular cause[a]	8	4.5%	3	1.7%	27	20.5%	72	44.6%	15	31.0%	25	62.4%
Repeat hospitalization[b]	12	6.9%	18	10.2%	35	27.0%	70	53.9%	15	35.0%	24	72.5%
Death from any cause or repeat hospitalization[b]	21	11.7%	22	12.3%	62	44.1%	117	71.6%	31	56.7%	45	87.9%
TIA[d]	0	0.0%	0	0.0%	1	0.7%	0	0.0%	2	2.5%	0	0.0%
All Stroke[c]	13	7.3%	3	1.7%	6	11.2%	5	5.5%	3	13.8%	0	5.5%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	1	0.8%	1	0.7%	1	1.6%	1	2.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Hemorrhagic Vascular Complication[f]	46	25.8%	10	5.7%	16	34.3%	16	17.7%	8	39.8%	5	22.9%
Major Vascular Complication[i]	30	16.8%	2	1.1%	2	17.4%	2	2.8%	0	17.4%	0	2.8%
Renal Failure[h]	2	1.1%	3	1.7%	2	2.3%	4	4.7%	1	3.2%	3	7.6%
Renal Insufficiency	8	4.6%	1	0.6%	4	7.3%	5	4.2%	3	9.9%	4	9.6%
Bleeding Events[e]	29	16.2%	4	2.2%	2	17.3%	0	2.2%	0	17.3%	0	2.2%
Cardiac reintervention												
Balloon aortic valvuloplasty	3	1.7%	11	6.1%	0	1.7%	41	29.1%	2	3.4%	7	33.0%
Repeat TAVR[e]	3	N/A	N/A	N/A	0	N/A	N/A	N/A	0	N/A	N/A	N/A
Aortic-valve replacement	0	0.0%	4	2.3%	0	0.0%	6	7.6%	1	0.9%	1	8.9%
Endocarditis	0	0.0%	0	0.0%	2	1.4%	1	0.8%	1	2.3%	0	0.8%
New Atrial Fibrillation[j]	13	N/A	13	N/A	3	N/A	8	N/A	N/A	N/A	N/A	N/A
New pacemaker	6	3.4%	9	5.1%	2	4.7%	5	8.6%	2	6.4%	0	8.6%

*Kaplan-Meier event rates are reported at 30 days,one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral

ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 9: NRCA (Cohort A) - Baseline Characteristics of the Patients and Echocardiographic Findings* (AT Population)			
Characteristic	Pooled (N=1521)	TA (N=822)	TF (N=699)
Age - years	85.5 ± 6.3	84.7 ± 6.3	86.3 ± 6.2
Male sex - no./total no. (%)	777/1519 (51.2%)	383/822 (46.6%)	394/697 (56.5%)
STS score	11.8 ± 3.8	12.2 ± 4.5	11.3 ± 2.8
Logistic EuroSCORE	28.4 ± 47.7	28.4 ± 16.6	28.5 ± 68.5
NYHA class - no./total no. (%)	1518/1518 (100.0%)	822/822 (100.0%)	696/696 (100.0%)
II	70/1518 (4.6%)	43/822 (5.2%)	27/696 (3.9%)
III	724/1518 (47.7%)	411/822 (50.0%)	313/696 (45.0%)
IV	722/1518 (47.6%)	368/822 (44.8%)	354/696 (50.9%)
Coronary artery disease - no./total no. (%)	1213/1518 (79.9%)	690/821 (84.0%)	523/697 (75.0%)
Previous MI - no./total no. (%)	399/1511 (26.4%)	236/819 (28.8%)	163/692 (23.6%)
Prior CABG - no./total no. (%)	670/1519 (44.1%)	416/822 (50.6%)	254/697 (36.4%)
Prior PCI - no./total no. (%)	665/1518 (43.8%)	391/821 (47.6%)	274/697 (39.3%)
Prior BAV - no./total no. (%)	400/1509 (26.5%)	242/818 (29.6%)	158/691 (22.9%)
Peripheral vascular disease - no./total no. (%)	694/1502 (46.2%)	495/813 (60.9%)	199/689 (28.9%)
Cerebral vascular disease - no./total no. (%)	400/1499 (26.7%)	248/812 (30.5%)	152/687 (22.1%)
COPD - no./total no. (%)			
Any	657/1521 (43.2%)	371/822 (45.1%)	286/699 (40.9%)
Oxygen dependent	174/904 (19.2%)	89/507 (17.6%)	85/397 (21.4%)
Creatinine > 2mg/dL - no./total no. (%)	139/1503 (9.2%)	73/815 (9.0%)	66/688 (9.6%)
Atrial fibrillation - no./total no. (%)	120/279 (43.0%)	56/133 (42.1%)	64/146 (43.8%)
Permanent pacemaker - no./total no. (%)	345/1517 (22.7%)	178/820 (21.7%)	167/697 (24.0%)
Pulmonary hypertension - no./total no. (%)	553/1514 (36.5%)	291/819 (35.5%)	262/695 (37.7%)
Frailty - no./total no. (%)	157/1515 (10.4%)	83/819 (10.1%)	74/696 (10.6%)
Extensively calcified aorta - no./total no. (%)	16/1515 (1.1%)	13/819 (1.6%)	3/696 (0.4%)
Deleterious effects of chest-wall irradiation - no./total no. (%)	6/1515 (0.4%)	3/819 (0.4%)	3/696 (0.4%)
Chest-wall deformity - no./total no. (%)	7/1515 (0.5%)	3/819 (0.4%)	4/696 (0.6%)
Liver disease - no./total no. (%)	37/1516 (2.4%)	22/820 (2.7%)	15/696 (2.2%)
Echocardiographic Findings			
Aortic valve area - cm^2	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2
Mean aortic valve gradient - mm Hg	44.6 ± 15.0	44.0 ± 15.1	45.2 ± 14.9
Mean LVEF - %	53.0 ± 13.0	53.3 ± 12.8	52.6 ± 13.3
Moderate or severe MR - no./total no. (%)	144/640 (22.5%)	72/335 (21.5%)	72/305 (23.6%)

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.
¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 10: NRCA (Cohort A) Procedure Data (AT Population)		
	TA NRCA	TF NRCA
Variable		
Total time of procedure (min)	235.51	219.34
Skin to skin time (min)	121.78	114.37
Fluoroscopy time (min)	14.75	25.16
Volume of contrast (ml)	101.35	139.78
Use of CPB	10.4%	1.4%
Use of general anesthesia	99.9%	99.9%
# of devices used		
0	8.8%	9.9%
1	87.2%	85.3%
2	3.6%	4.6%
3	0.4%	0.3%
Valve in valve procedure	2.1%	2.1%
Valve Size		
19 mm	N/A	N/A
21 mm	N/A	N/A
22 mm	N/A	N/A
23 mm	53.4%	52.5%
25 mm	N/A	N/A
26 mm	46.6%	47.3%
27 mm	N/A	N/A
29 mm	N/A	1 (0.1%)
Adverse event during procedure	17.6%	23.1%
Device malfunction	0.5%	0.6%
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	39.8%	39.1%
Procedure Success (Device success, no MACCE < 30d)	38.0%	36.9%

Table 11: Randomized v. Nonrandomized (Cohort A) - Clinical Outcomes up to 1 Year (AT Population)

	0 -30 Days										31 Days - 1 Year									
	PMA Pooled		PMA TA		PMA TF		Transfemoral Approach NRCA TF		Transapical Approach NRCA TA		PMA Pooled		PMA TA		PMA TF		Transfemoral Approach NRCA TF		Transapical Approach NRCA TA	
Outcome (NRCA)	Pooled	KM Pooled	TA	KM TA	TF	KM TF	TF	KM Event rate TF	TA	KM Event rate TA	Pooled	KM Pooled	TA	KM TA	TF	KM TF	TF	KM Event rate TF	TA	KM Event rate TA
Death	18	5.2%	9	8.7%	9	3.7%	22	3.2%	66	8.2%	63	23.7%	21	29.1%	42	21.4%	74	19.4%	82	23.6%
Death from cardiovascular cause[a]	14	4.1%	6	5.8%	8	3.3%	16	2.3%	46	5.7%	30	13.6%	11	17.4%	19	12.0%	51	14.2%	48	15.3%
Death from any cause or repeat hospitalization[b]	35	10.2%	14	13.5%	21	8.7%	41	6.0%	86	10.8%	86	33.9%	27	38.7%	59	31.8%	99	25.8%	115	30.7%
All Stroke[c]	15	4.4%	7	7.0%	8	3.3%	30	4.4%	16	2.0%	4	5.8%	3	10.8%	1	3.8%	6	5.7%	6	3.7%

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

Figures – Cohort A

Figure 3. COHORT A - Primary Endpoint
All Cause Mortality (AT Population)
(68% confidence limits displayed)

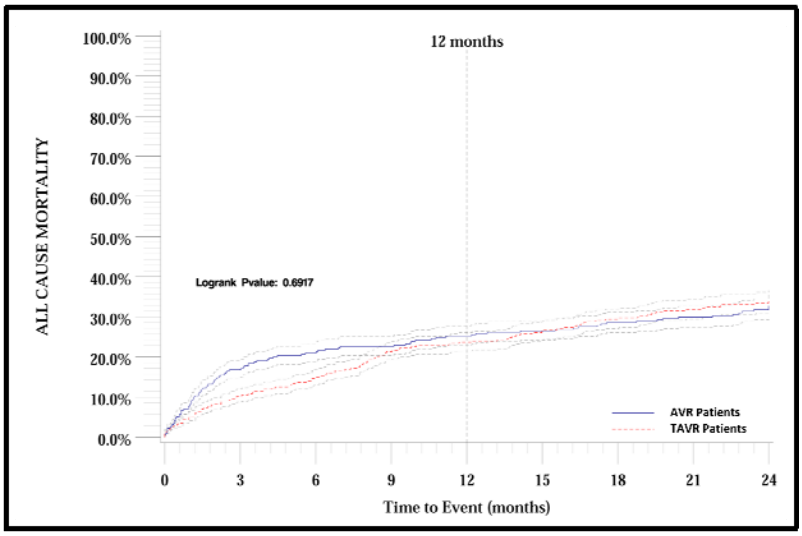


Figure 4. COHORT A - Secondary Endpoint
Mortality or Repeat Hospitalization (AT Population)
(68% confidence limits displayed)

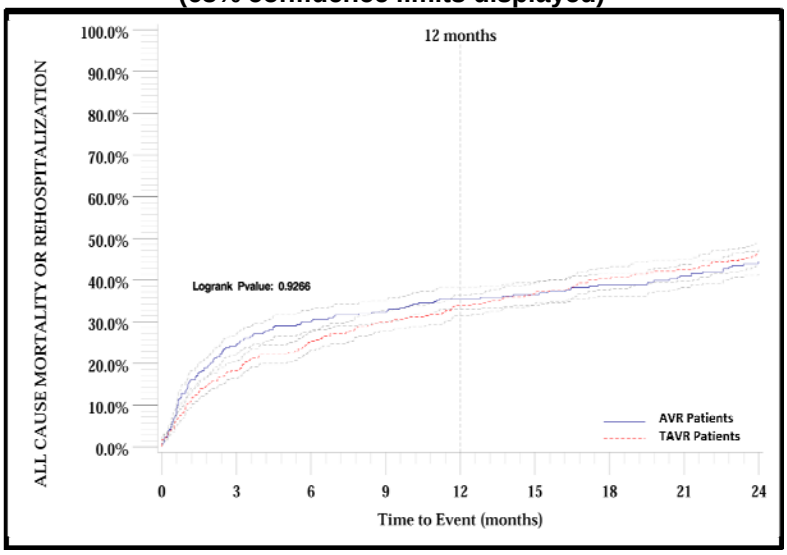


**Figure 5. COHORT A – Secondary Endpoint:
Death from Cardiovascular Cause (AT Population)
(68% confidence limits displayed)**

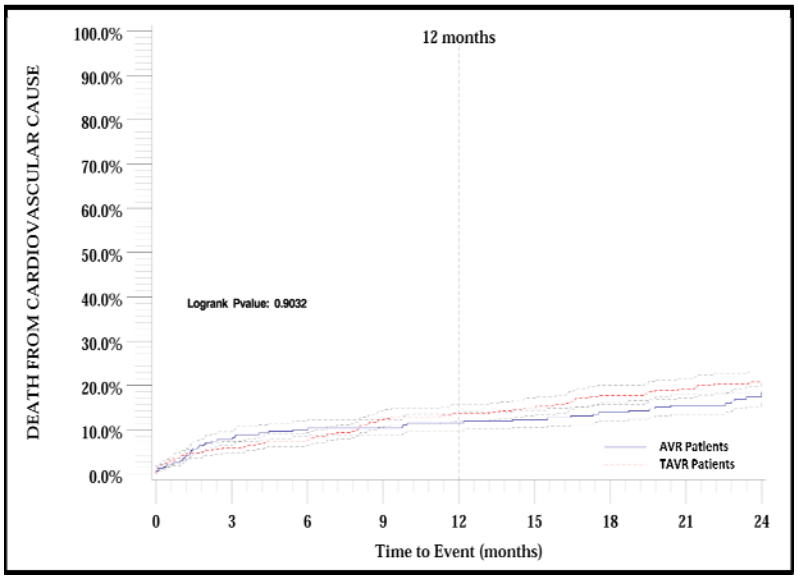


**Figure 6. COHORT A - Secondary Endpoint:
AVA Over Time (AT Population)
(one standard deviation displayed)**

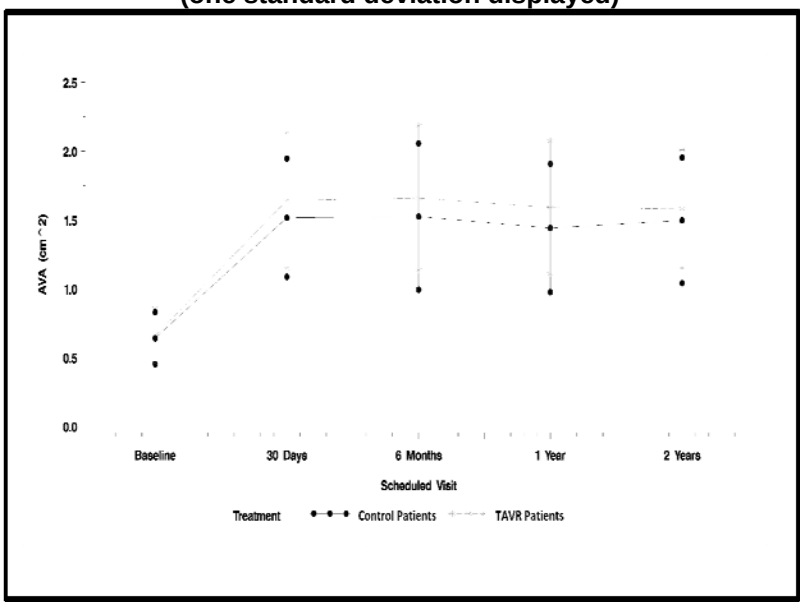


**Figure 7. COHORT A - Secondary Endpoint:
Mean Gradient Over Time (AT Population)
(one standard deviation displayed)**

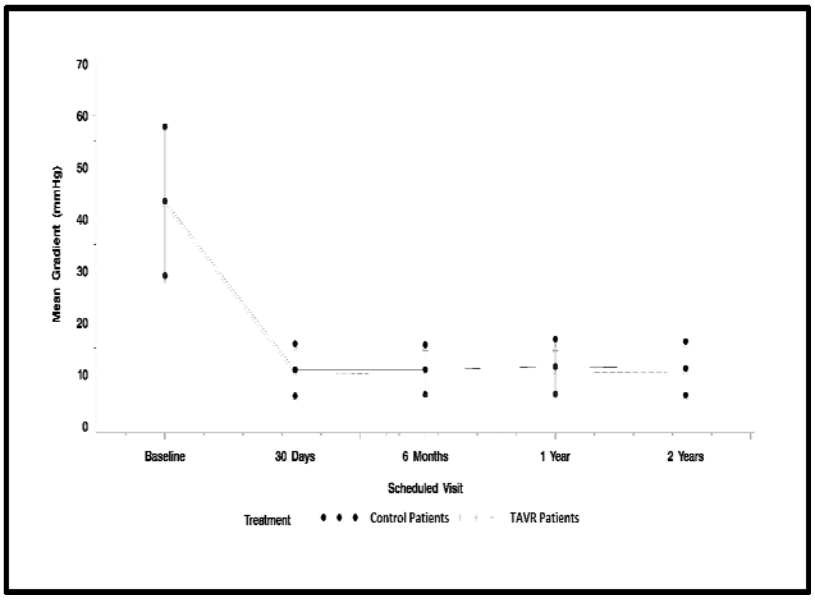
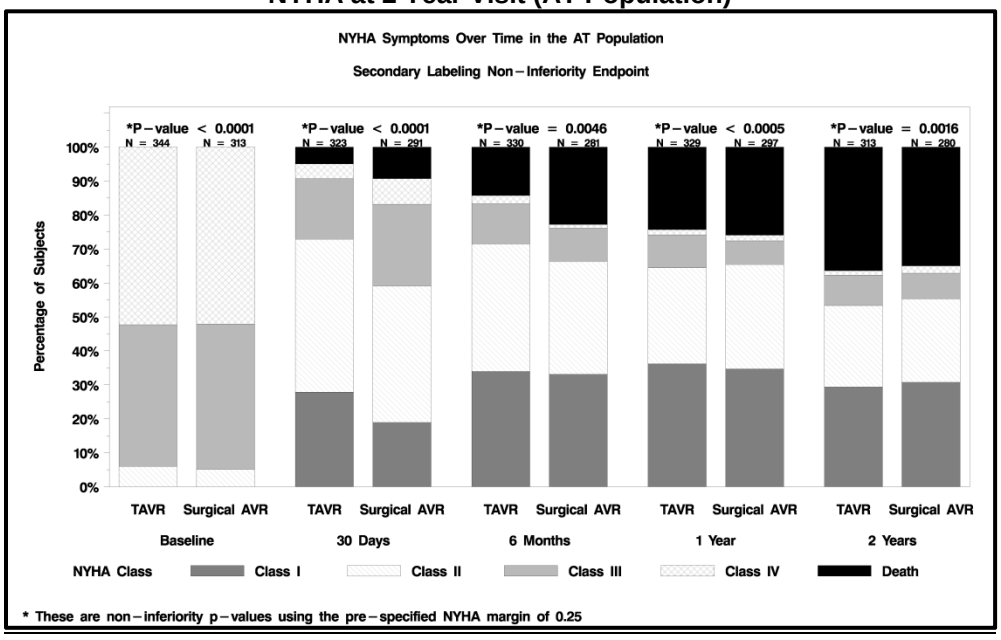


**Figure 8. COHORT A- Secondary Endpoint:
NYHA at 2 Year Visit (AT Population)**



Figures – Cohort B

Figure 9. COHORT B - Primary Endpoint
All Cause Mortality (ITT Population)
(68% confidence limits displayed)

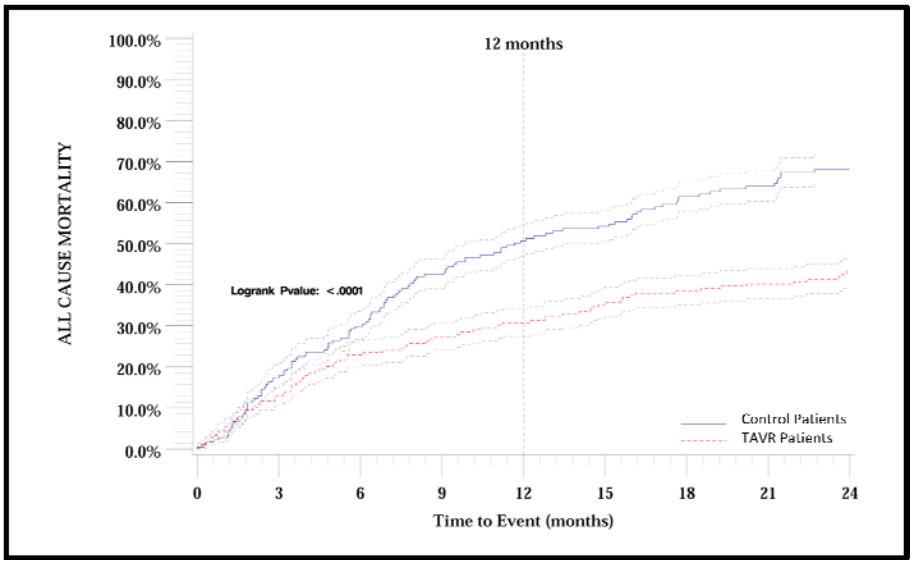


Figure 10. COHORT B - Co-Primary Endpoint
Mortality or Repeat Hospitalization (ITT Population)
(68% confidence limits displayed)

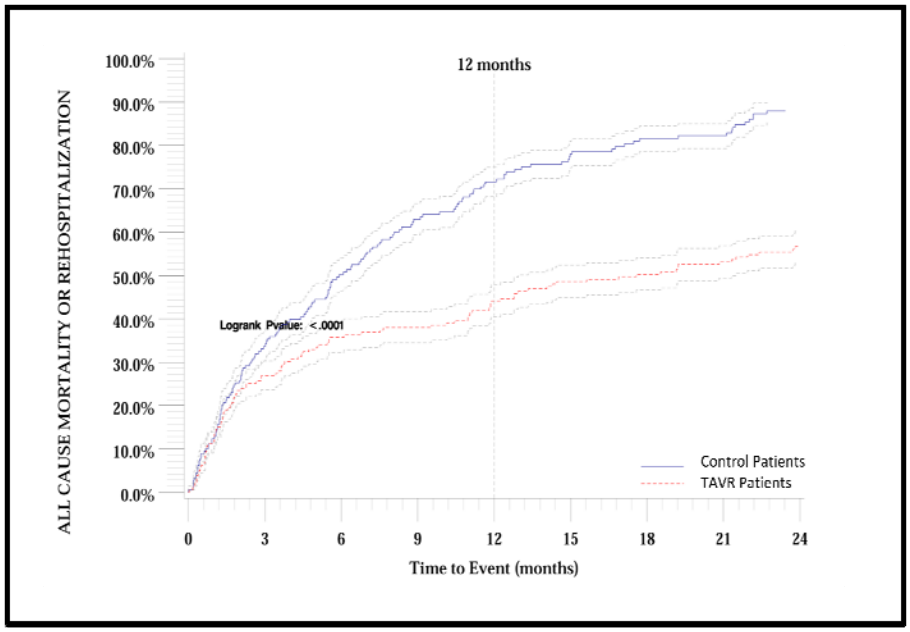


Figure 11. COHORT B – Secondary Endpoint
Death from Cardiovascular Cause (ITT Population)
(68% confidence limits displayed)

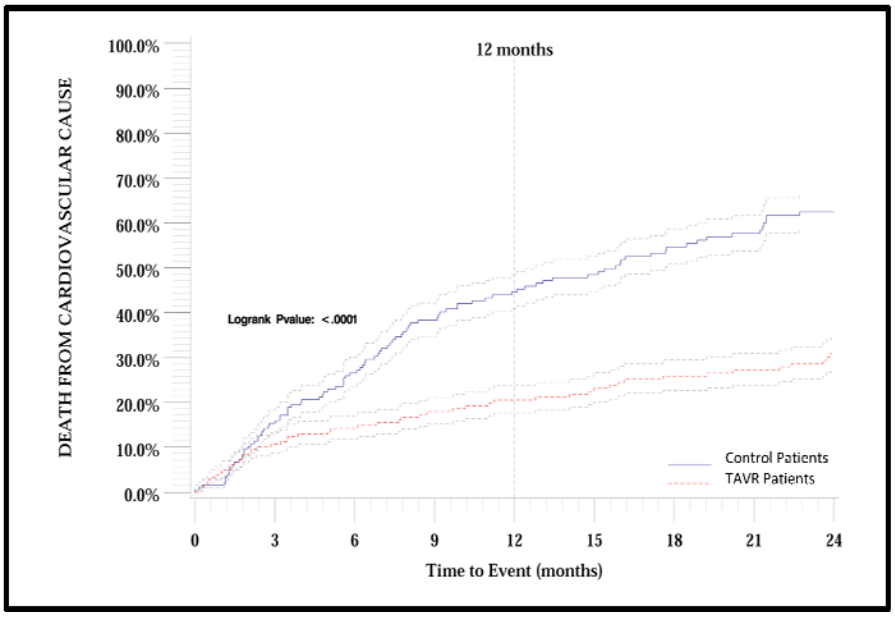


Figure 12. COHORT B - Secondary Endpoint:
AVA Over Time (ITT Population)
(one standard deviation displayed)

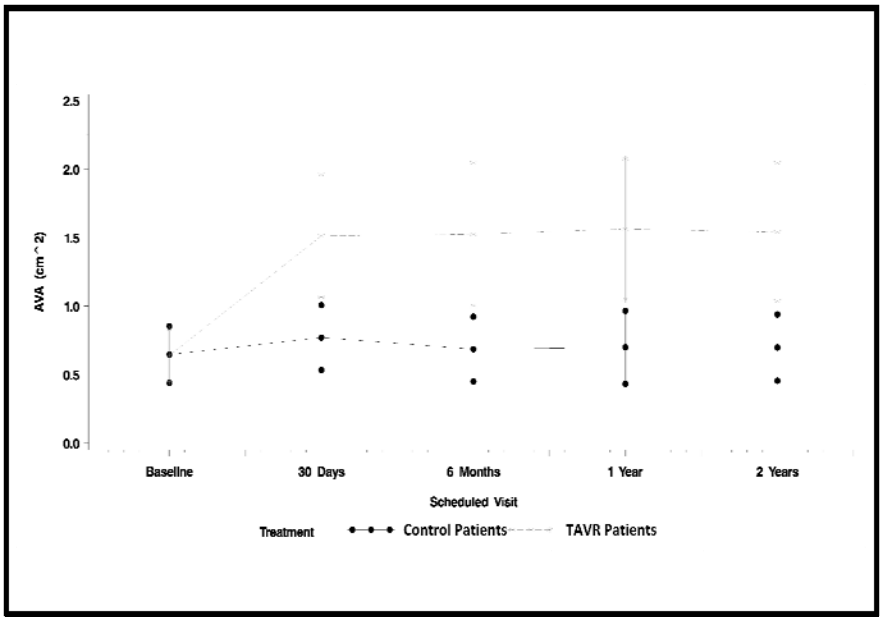


**Figure 13. COHORT B- Secondary Endpoint:
Mean Gradient Over Time (ITT Population)
(one standard deviation displayed)**

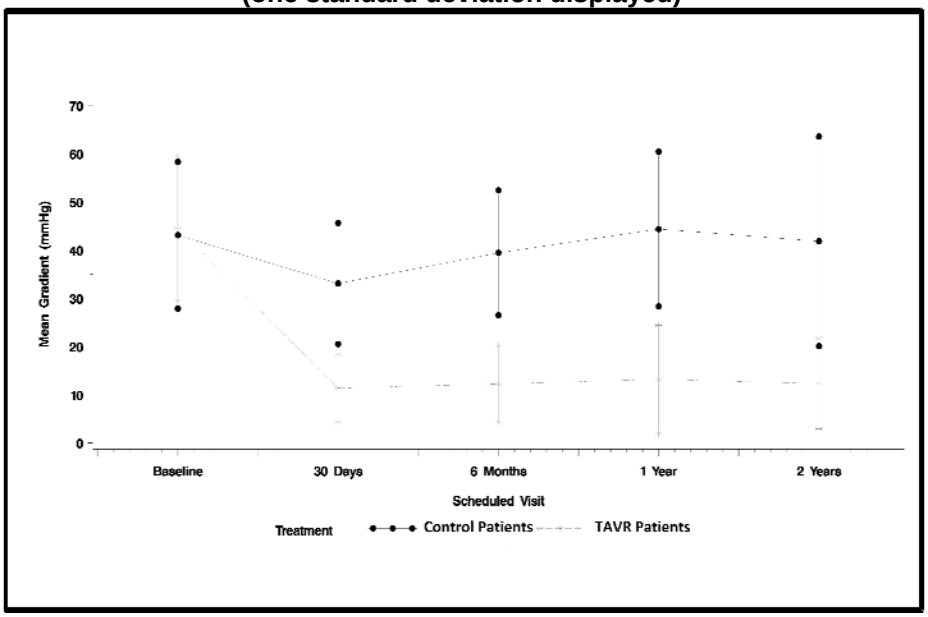
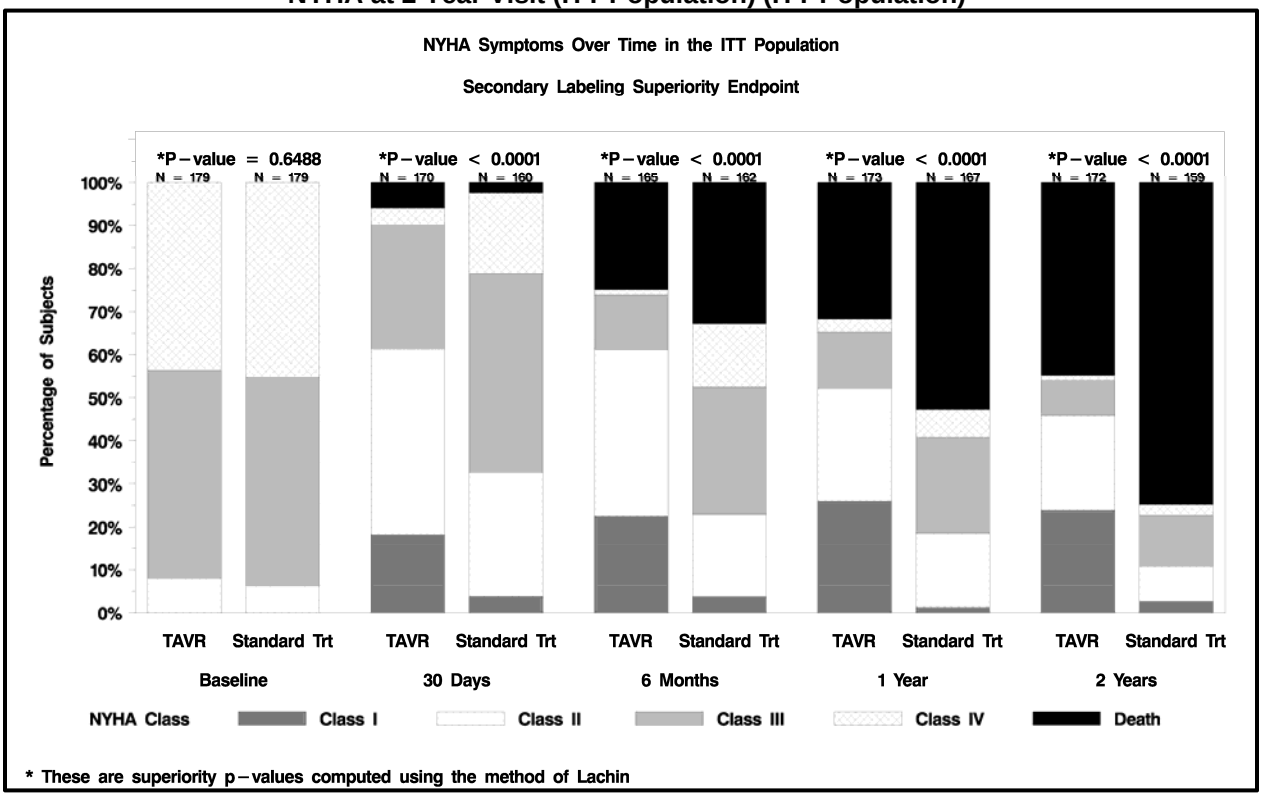


**Figure 14. COHORT B- Secondary Endpoint:
NYHA at 2 Year Visit (ITT Population) (ITT Population)**



Figures – Cohort A Non Randomized Continued Access (NRCA)

Figure 15. All Cause Mortality:
Comparison of NRCA Patients to Pooled Randomized Patients (AT Population)
(68% confidence limits displayed)

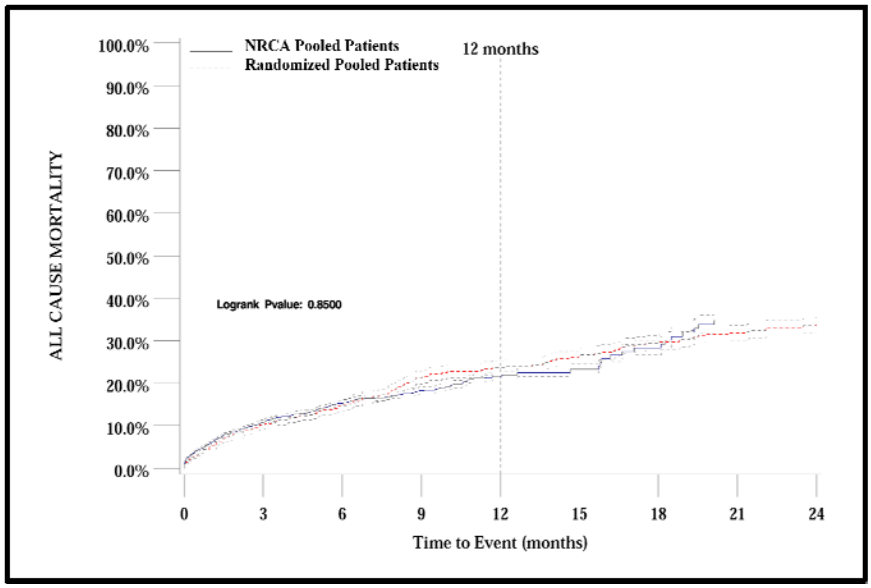


Figure 16. Stroke:
Comparison of NRCA Patients to Pooled Randomized Patients (AT Population)
(68% confidence limits displayed)

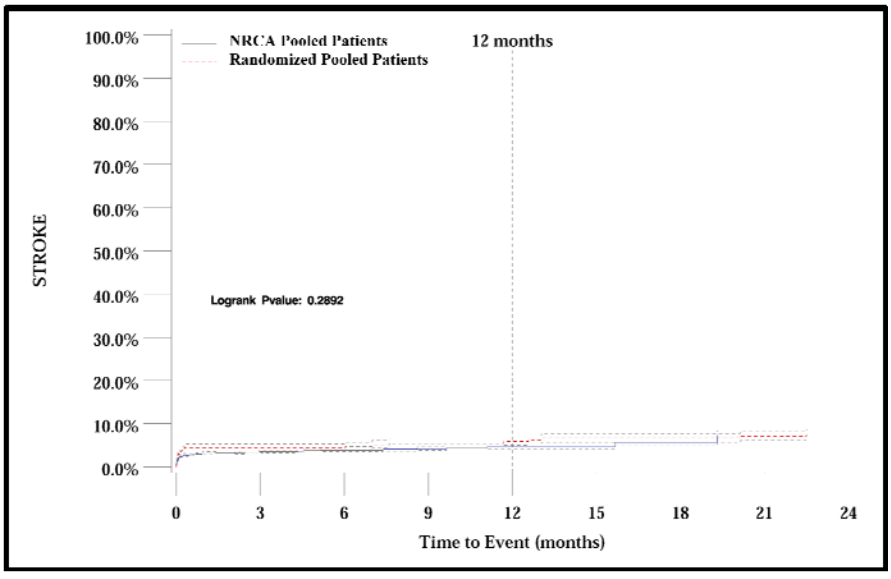


Figure 17. All Cause Mortality:
Comparison of NRCA Patients to Randomized TF Patients (AT Population)
(68% confidence limits displayed)

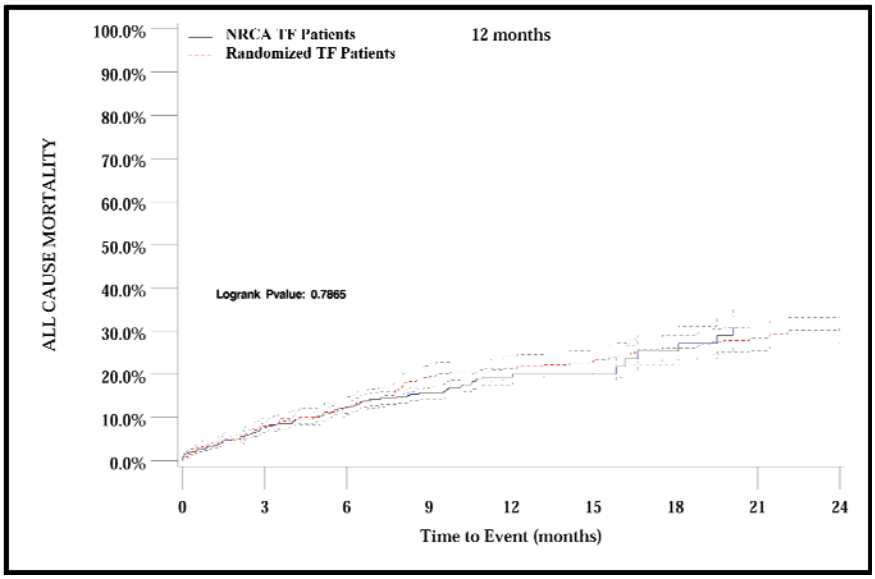


Figure 18. Stroke:
Comparison of NRCA Patients to Randomized TF Patients (AT Population)
(68% confidence limits displayed)

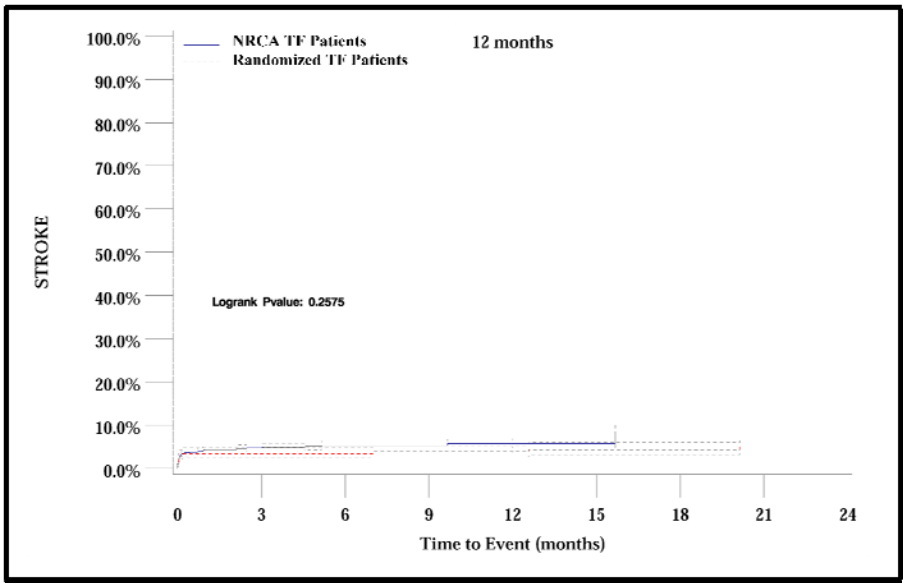


Figure 19. All Cause Mortality:
Comparison of NRCA Patients to Randomized TA Patients (AT Population)
(68% confidence limits displayed)

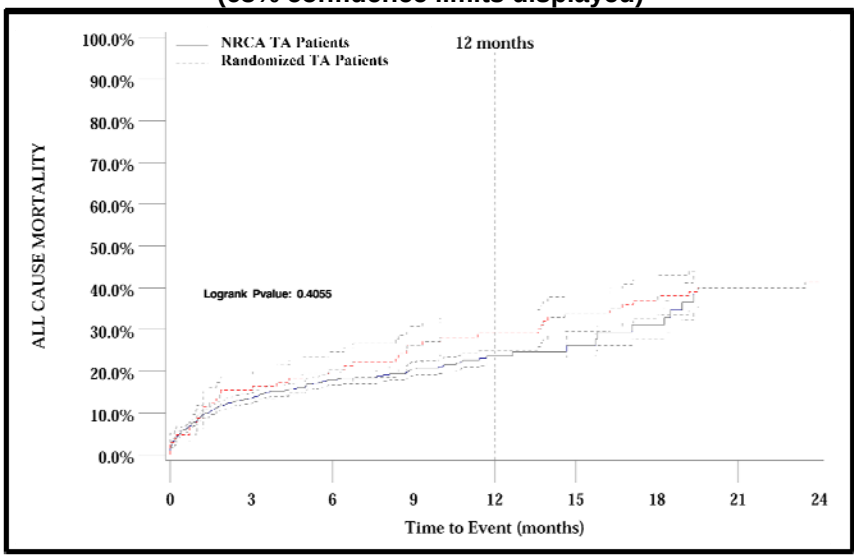
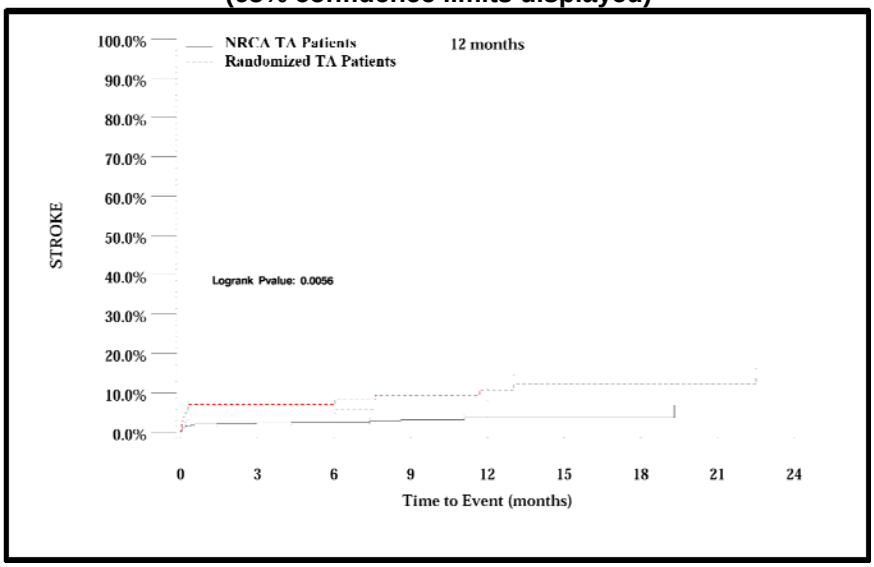


Figure 20. Stroke:
Comparison of NRCA Patients to Randomized TA Patients (AT Population)
(68% confidence limits displayed)



Ascendra Balloon Aortic Valvuloplasty Catheter

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device.

1.0 Device Description

The Ascendra Balloon Aortic Valvuloplasty Catheter (Figure 1 on page 2) consists of a shaft and balloon with radiopaque marker bands indicating working length of the balloon. At the proximal end of the device, there is a standard "Y-connector" for balloon inflation and the guidewire lumen. An extension tubing is supplied for use with the balloon valvuloplasty catheter during inflation. The inflation parameters are as follows:

Table 1. Inflation Parameters

Model	Nominal	
	Balloon Dimensions	Inflation Volume w/extension tubing
9100BAVC	20 mm x 3 cm	15 mL

Device Compatibility:

- Maximum guidewire diameter: 0.035" (0.89 mm)
- Minimum sheath compatibility: 14F (4.62 mm)

Note: For proper volume sizing, the balloon valvuloplasty catheter should be used with the inflation device provided by Edwards Lifesciences.

2.0 Indications

The Ascendra Balloon Aortic Valvuloplasty Catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of a transcatheter heart valve.

3.0 Contraindications

Other than standard risks associated with insertion of a cardiovascular catheter, there are no known contraindications for valvuloplasty. The patient's medical condition could affect successful use of this catheter.

4.0 Warnings

- The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not mishandle the device or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.

5.0 Precautions

- For special considerations associated with the use of this device prior to transcatheter heart valve implantation, refer to the bioprosthesis instructions for use (IFU).
- Use only appropriate balloon inflation medium. Do not use air or gaseous medium to inflate the balloon.
- The device is not intended for post-dilation of deployed transcatheter heart valves.
- While exposed within the body, device advancement and retrieval should not be done without the aid of fluoroscopy. Do not advance or retract the device unless the balloon is fully deflated under vacuum.

6.0 Potential Adverse Events

Complications associated with standard catheterization, balloon valvuloplasty, and the use of angiography include, but are not limited to, allergic reaction to anesthesia or to contrast media, thrombus formation, plaque dislodgement and embolization that may result in myocardial infarction, stroke, distal peripheral occlusion and/or death, arrhythmia development, cardiac perforation, conduction system injury, hematoma, infundibulum injury, annular tear or rupture and/or valve leaflet dehiscence, severe valve insufficiency, valve restenosis, valve damage, balloon rupture.

7.0 Directions for Use

Step	Procedure
1	Prepare access site for balloon valvuloplasty catheter insertion and position guidewire using standard techniques.
2	Flush the guidewire lumen with heparinized solution. Attach the extension tubing to the balloon inflation port.
3	Prepare the inflation device with diluted contrast solution (15:85 contrast to heparinized saline) and attach to the extension tubing.
4	Induce a negative pressure to remove any air from the balloon and inflation lumen. Repeat until all air is expelled. Close the stopcock to the balloon valvuloplasty catheter, ensuring the system is maintained at negative pressure.

Step	Procedure
5	Fill the inflation device with the appropriate volume of diluted contrast medium.
6	Open the stopcock to the balloon valvuloplasty catheter. Allow the inflation lumen to fill with the diluted contrast medium. Maintain at neutral pressure. Lock the inflation device.
7	Remove balloon cover.
8	Advance the balloon valvuloplasty catheter over the guidewire, through the introducer sheath, across the valve, and position the balloon at the intended site utilizing the radiopaque markers. Unlock the inflation device.
9	Fully inflate the balloon with the inflation device.
10	Completely deflate the balloon, and gently withdraw the balloon valvuloplasty catheter and remove from the sheath.

8.0 How Supplied

Supplied pouched and sterilized by ethylene oxide.

9.0 Storage

The Ascendra Balloon Aortic Valvuloplasty Catheter should be stored in a cool, dry place.

10.0 Device Disposal

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

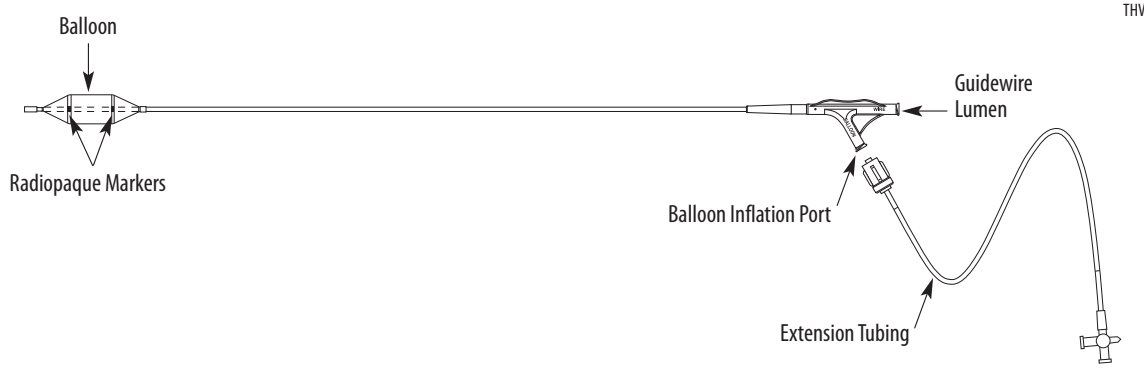


Figure 1. Ascendra Balloon Aortic Valvuloplasty Catheter

Edwards

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One Edwards Way
Irvine, CA 92614-5686 USA
Made in USA

Telephone 949.250.2500
800.424.3278
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Web IFU
199941001 A

Ascendra Introducer Sheath Set

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device.

1.0 Device Description

The Ascendra Introducer Sheath Set (Figure 1 on page 2) contains an introducer and sheath. The sheath has a radiopaque marker for visualization of the tip and non-radiopaque depth markings on the distal end of the body of the sheath. The proximal end of the sheath includes a side port. The introducer has a radiopaque marker at the distal end where the taper begins.

Model	Minimum Sheath I.D.
9100IS	26F (8.5 mm)

2.0 Indications

The Ascendra Introducer Sheath Set is indicated for the introduction and removal of devices used with the Edwards SAPIEN Transcatheter Heart Valve.

3.0 Contraindications

Apical left ventricular aneurysm.

4.0 Warnings

The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.

Do not mishandle the device or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.

The Ascendra Introducer Sheath Set must be used with a 0.035" guidewire.

5.0 Precautions

No known precautions.

6.0 Potential Adverse Events

Complications associated with cardiac surgical intervention and use of angiography include, but are not limited to, allergic reaction to anesthesia or to contrast media, injury including myocardial injury, thrombus formation, and plaque dislodgement which may result in myocardial infarction, arrhythmia, stroke, and/or death.

7.0 Directions for Use

Step	Procedure
1	Gain access to the left ventricular apex via a mini left anterior thoracotomy.
2	Place at least two pledgeted sutures (e.g. purse-string or mattress) around the access site.
3	Hydrate the length of the introducer and sheath. Flush the sheath and introducer using heparinized saline.
4	Fully insert the introducer into the sheath and flush the sheath again. Close the stopcock to the sheath.
5	Insert an 18G needle within the sutures and insert a 0.035" soft guidewire through the needle. Exchange needle for a 14F introducer sheath and cross the native valve with soft guidewire. Exchange soft guidewire for exchange length extra stiff guidewire.
6	Using the sheath depth markers, advance the introducer sheath over the guidewire to the desired depth in the left ventricle while following its progression on fluoroscopy.
7	Remove the introducer from the sheath to provide access for entry and/or removal of a device. Continue to hold the guidewire centered relative to the introducer sheath.
8	Upon completion of the procedure, remove the sheath from the access site, close the access site and confirm hemostasis.

8.0 How Supplied

The Ascendra Introducer Sheath Set is supplied pouched and sterilized by ethylene oxide.

9.0 Storage

The Ascendra Introducer Sheath Set should be stored in a cool, dry place.

10.0 Device Disposal

Used introducer sheath sets may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

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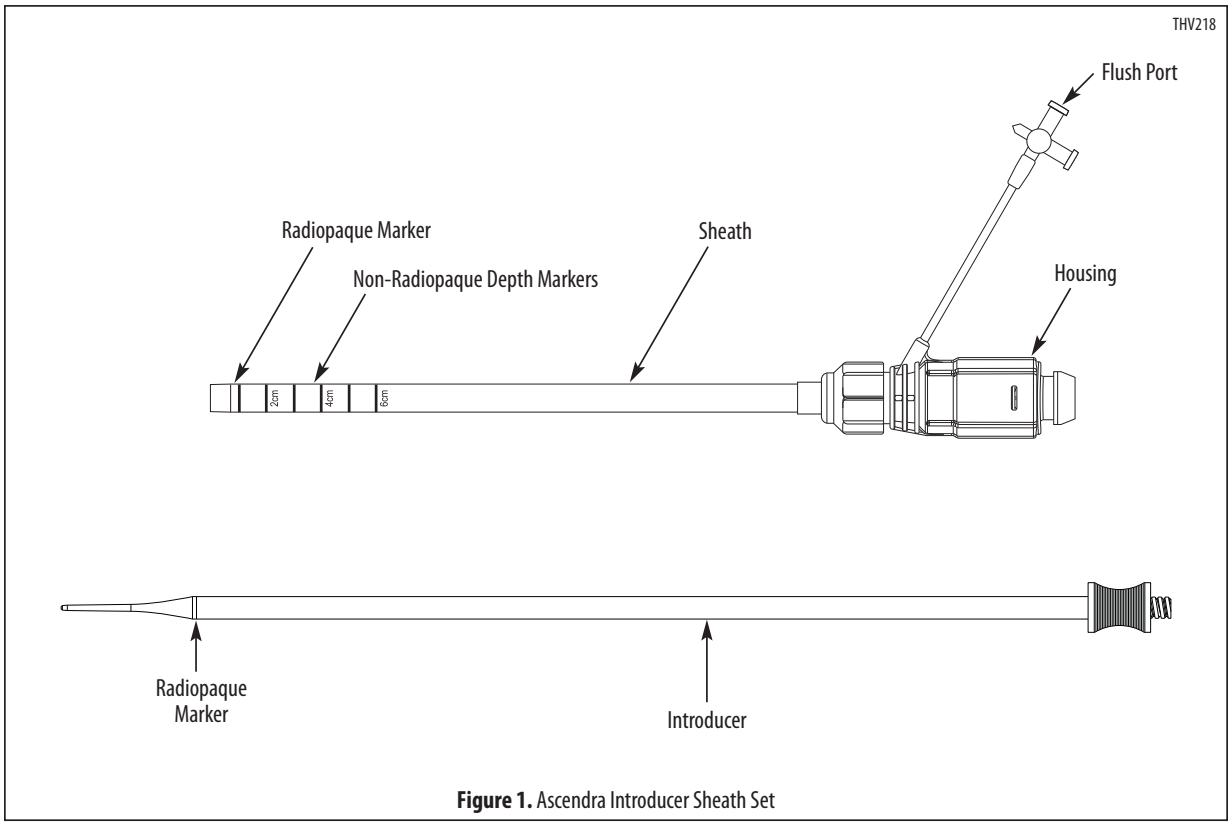

Figure 1. Ascendra Introducer Sheath Set

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Edwards SAPIEN Transcatheter Heart Valve with the RetroFlex 3 Delivery System

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Transfemoral Retrograde Approach

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

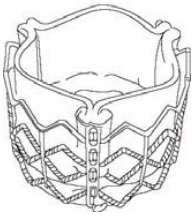
STERILE: The bioprosthesis is supplied sterilized with gluteraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

1.0 Device Description

- Edwards SAPIEN Transcatheter Heart Valve – Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve (bioprosthesis) is comprised of a balloon-expandable, radiopaque, stainless steel (316 L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde.

Figure 1. Edwards SAPIEN Transcatheter Heart Valve



Bioprosthesis Diameter	Frame Height (Profile)
23 mm	14.3 mm
26 mm	16.1 mm

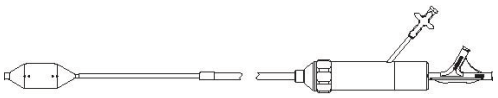
The following table identifies the bioprosthesis size that should be used based on native valve annulus size, as measured by transesophageal echocardiography (TEE).

Native Valve Annulus Size (Tissue Annulus Diameter)	Bioprosthesis Diameter
18-22 mm	23 mm
21-25 mm	26 mm

- RetroFlex 3 Delivery System – Model 9120FS23 for 23 mm valve procedure and 9120FS26 for 26 mm valve procedure (Figure 2)

The RetroFlex 3 delivery system includes a rotating wheel within the handle for articulation of the flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon for deployment of the bioprosthesis, and radiopaque markers as indicated in Figure 2.

Figure 2. RetroFlex 3 Delivery System



Black dots indicate position of radiopaque markers.

Nominal Balloon Diameter	RBP
23 mm	7 ATM (709 kPa)
26 mm	7 ATM (709 kPa)

The following table identifies the access vessel diameters that should be used for delivery system access.

Ilio-Femoral Vessel Diameter	Delivery System
≥ 7 mm	23 mm
≥ 8 mm	26 mm

2.0 Indications

The Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, is indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by two cardiac surgeons to be inoperable, or at high risk for surgical aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis. The RetroFlex 3 Delivery System is indicated for the transfemoral delivery of the Edwards SAPIEN Transcatheter Heart Valve.

3.0 Contraindications

The bioprosthesis and delivery system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There is an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments.
- The devices are designed, intended, and distributed for single use only. **Do not re-sterilize or reuse the devices.** There are no data to support the sterility, non-pyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the bioprosthesis may lead to paravalvular leak, migration, embolization and/or annular rupture.
- Accelerated deterioration of the bioprosthesis may occur in patients with an altered calcium metabolism. Bioprosthesis must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Bioprosthesis leaflets mishandled or damaged during any part of the procedure will require replacement of the bioprosthesis.
- Caution should be exercised in implanting a bioprosthesis in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the bioprosthesis to ensure proper bioprosthesis positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Do not use the bioprosthesis if the tamper evident seal is broken, the storage solution does not completely cover the bioprosthesis, the temperature indicator has been activated, the bioprosthesis is damaged, or the expiration date has elapsed.
- Do not mishandle the RetroFlex 3 delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.
- Patient injury could occur if the delivery system is not un-flexed prior to removal.
- Care should be exercised in patients with hypersensitivities to chromium, nickel, molybdenum, manganese, copper, silicon, and/or polymeric materials.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.

5.0 Precautions

- Long-term durability has not been established for the bioprosthesis. Regular medical follow-up is advised to evaluate bioprosthesis performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Bioprosthetic valve recipients should be maintained on anticoagulant and antiplatelet therapy (e.g. clopidogrel or ticlopidine [75 mg/day]) for 6 months post procedure and aspirin (75-100 mg/day) for life, except when contraindicated, as determined by their physician.
- The safety of the bioprosthesis implantation has not been established in patients who have:
  - Pre-existing prosthetic heart valve in the aortic position
  - Severe ventricular dysfunction with ejection

fraction <20%

- Hypertrophic cardiomyopathy with or without obstruction (HOCM)

- Safety, effectiveness, and durability have not been established for valve-in-valve procedures.
- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
  - Non-calcified aortic annulus
  - Congenital unicuspid or congenital bicuspid aortic valve
  - Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+)
  - Pre-existing prosthetic heart valve or prosthetic ring in any position
  - Severe mitral annular calcification (MAC), severe (>3+) mitral insufficiency, or Gorelin syndrome
  - Blood dyscrasias defined as: leukopenia (WBC<3000 mm^3), acute anemia (Hb <9 mg%), thrombocytopenia (platelet count <50,000 cells/mm^3), or history of bleeding diathesis or coagulopathy
  - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
  - Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
  - A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated
  - Native aortic annulus size <18 mm or >25 mm as measured by echocardiogram
  - Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta
  - Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter
  - Bulky calcified aortic valve leaflets in close proximity to coronary ostia

6.0 Potential Adverse Events

- Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization for the transfemoral access procedure, balloon valvuloplasty, and the potential risks of local and/or general anesthesia:
  - Death
  - Stroke/transient ischemic attack clusters or neurological deficit
  - Paralysis
  - Permanent disability
  - Respiratory insufficiency or respiratory failure
  - Hemorrhage requiring transfusion or intervention
  - Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
  - Pericardial effusion or cardiac tamponade
  - Embolization including air, calcific valve material or thrombus
  - Infection including septicemia and endocarditis
  - Heart failure
  - Myocardial infarction
  - Renal insufficiency or renal failure
  - Conduction system injury (defect) which may require a permanent pacemaker
  - Arrhythmia
  - Retroperitoneal bleed
  - Femoral AV fistula or pseudoaneurysm
  - Reoperation
  - Peripheral ischemia or nerve injury
  - Restenosis
  - Pulmonary edema
  - Pleural effusion
  - Bleeding
  - Anemia
  - Abnormal lab values (including electrolyte imbalance)
  - Hypertension or hypotension
  - Allergic reaction to anesthesia or to contrast media
  - Hematoma
  - Syncope
  - Pain or changes at the access site
  - Exercise intolerance or weakness
  - Inflammation
  - Angina
  - Heart murmur
  - Fever
  - Mechanical failure of delivery system and/or accessories

- Additional potential risks specifically associated with the use of the bioprosthesis include, but may not be limited to the following:
  - Cardiac arrest
  - Cardiogenic shock
  - Emergency cardiac surgery
  - Cardiac failure or low cardiac output
  - Coronary flow obstruction/transvalvular flow disturbance
  - Device thrombosis requiring intervention
  - Valve thrombosis
  - Device embolization
  - Device migration or malposition requiring intervention
  - Valve deployment in unintended location
  - Valve stenosis
  - Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflets retraction, stent creep, suture line disruption of components of a prosthetic valve, thickening, stenosis)
  - Device degeneration
  - Paravalvular or transvalvular leak
  - Valve regurgitation
  - Hemolysis
  - Device explants
  - Nonstructural dysfunction
  - Non-emergent reoperation

All listed risks may include symptoms associated with the above mentioned medical conditions.

7.0 Directions for Use

7.1 Required Equipment

- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, and 15% diluted radiopaque contrast medium
- 20 cc or larger luer-lock syringe
- 60 cc or larger luer-lock syringe
- High-pressure 3-way stopcock
- Edwards SAPIEN Transcatheter Heart Valve
- RetroFlex 3 Delivery System
- 20 mm and/or 23 mm balloon catheter such as: RetroFlex balloon catheter Model 9120BC20 for use prior to 23 mm valve implantation and Model 9120BC23 for use prior to 26 mm valve implantation
- RetroFlex 3 Introducer Sheath Set Model 9120S23 for 23 mm valve procedure and Model 9120S26 for 26 mm valve procedure
- RetroFlex Dilator Kit Model 9100DKS7
- Crimper Model 9100CR23 for 23 mm valve procedure and Model 9100CR26 for 26 mm valve procedure
- Inflation device provided by Edwards Lifesciences for this application

7.2 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Bioprosthesis Rinsing Procedure

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Bioprosthetic valves from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number. Inspect the bioprosthesis for any signs of damage to the frame or tissue.
3	Rinse the bioprosthesis as follows: Place the bioprosthesis in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate (to **gently** swirl the bioprosthesis and holder) back and forth for a minimum of 1 minute. Transfer the bioprosthesis and holder to the second rinsing bowl of physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The bioprosthesis should be left in the final rinse solution

Step	Procedure
	until needed to prevent the tissue from drying. **CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls. The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.2.2 Prepare Transfemoral Procedure Components

Step	Procedure
1	Refer to RetroFlex Dilator Kit, RetroFlex 3 Introducer Sheath Set and Crimper instructions for use on device preparation and handling.
2	Prime and flush the guidewire lumen of the delivery system with heparinized saline.
3	Insert an extra stiff guidewire [0.035 inch (0.89 mm) and ≥ 150 cm long] in the guidewire lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
4	Flush the delivery system with heparinized saline through the flush port.
5	Place the loader cap onto the delivery system, ensuring that the inside of the loader cap is in the same direction as the tapered tip.
6	Prepare a 60 mL or larger luer-lock syringe with diluted contrast medium (15:85 contrast to heparinized saline) and attach it to a 3-way stopcock on the balloon inflation port.
7	Completely fill the inflation device provided by Edwards Lifesciences and attach to 3-way stopcock. Ensure there are no air bubbles in the balloon. If an air bubble is detected, eliminate it while deflating the balloon. Close the stopcock to the syringe.
8	Insert the balloon into the balloon gauge located on the crimper. Inflate the balloon and verify its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the gauge. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflating solution in the inflation device provided by Edwards Lifesciences until the correct diameter is reached. The inflation device must remain connected to the delivery system throughout the rest of the procedure.
	Note: Correct balloon sizing is critical to successful valve deployment and valve function.
9	Close stopcock to the delivery system and remove any remaining contrast solution in inflation device provided by Edwards Lifesciences. Lock the inflation device.
10	Close the stopcock to the 60 mL syringe and verify the balloon is sized appropriately with the gauge. Remove the syringe. Unlock inflation device provided by Edwards Lifesciences and deflate the balloon while creating a three-wing fold configuration, and ensure no fluid is left behind. Lock the inflation device provided by Edwards Lifesciences.

7.2.3 Mount and Crimp the Bioprosthesis on the Delivery System

Step	Procedure
1	Remove the bioprosthesis from the holder and gently place the bioprosthesis into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the delivery system with the inflow (fabric cuff end) of the bioprosthesis towards the distal end of the balloon catheter. Ensure that the inflow of the bioprosthesis is aligned with the proximal end of the tapered catheter tip.
4	Place the bioprosthesis back in the crimper aperture, and completely crimp until it fits inside the crimp gauge. **CAUTION: The physician must verify correct mounting/orientation of the bioprosthesis prior to its implantation.**
5	Press on the balloon shoulders circumferentially to facilitate insertion into the flex catheter and loader.
6	Pull the proximal end of the balloon into the flex catheter until the proximal edge of the bioprosthesis is flush against the distal end of the flex catheter.
7	Flush the loader with sterile heparinized saline and insert the crimped bioprosthesis inside the loader.
8	Advance the bioprosthesis into the loader until the distal end of the delivery system tip is exposed.
9	Screw the loader cap to the loader, re-flush the flex catheter and close the stopcock to the delivery system. **Note:** Keep bioprosthesis hydrated until ready for implantation.
10	Remove guidewire and flush guidewire

Step	Procedure
	lumen.

7.3 Valvuloplasty and Bioprosthesis Delivery

Valvuloplasty and bioprosthesis delivery should be performed under local and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

CAUTION: Use of the retrograde approach may require a femoral artery cut-down with surgical closure of the puncture site due to the large size of the arteriotomy.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Valvuloplasty

Refer to RetroFlex Balloon Catheter Instructions for Use (IFU) for information on device preparation and handling.

Note: Rapid ventricular pacing should be performed when using the RetroFlex balloon catheter for valvuloplasty prior to aortic transcatheter valve implantation.

After placement of the balloon at the intended site, begin rapid ventricular pacing. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Bioprosthesis Delivery

Step	Procedure
1	Dilate the femoro-iliac vessel using the RetroFlex dilator kit. Refer to RetroFlex Dilator Kit IFU for information on device preparation and handling.
2	Insert the introducer sheath. Refer to the RetroFlex 3 Introducer Sheath Set IFU for additional information on device preparation and handling.
3	Insert the loader into the sheath.
4	Push the delivery system through the sheath. **CAUTION: The bioprosthesis should not be advanced through the sheath if the sheath tip is not past the aortic bifurcation.**
5	Retract loader to the proximal end of RetroFlex 3 delivery system.
6	The catheter articulates in a direction opposite from the flush port, and the flush port should be pointed away from the physician. Advance the RetroFlex 3 delivery system up the descending aorta; deflect the delivery system by rotating its handle "clockwise".
7	Cross the native aortic valve and position the bioprosthesis within the diseased valve.
8	Maintain the position of the bioprosthesis and retract the flex catheter, leaving the bioprosthesis in position. Verify that the flex catheter is completely off of the balloon before it is inflated and the bioprosthesis is deployed.
9	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
10	Verify the correct location of the bioprosthesis with respect to the calcified valve.
11	Begin bioprosthesis deployment: • Unlock the inflation device. • Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the bioprosthesis by inflating the balloon with the entire volume in the inflation device. When the delivery system has been completely deflated, turn off the pacemaker. • De-articulate the delivery system and remove it from the sheath.

	CAUTION: Patient injury could occur if the delivery system is not un-flexed prior to removal.
12	Remove sheath when the ACT level is appropriate (e.g., reaches < 150 sec). Close puncture site.

8.0 How Supplied

STERILE: The bioprosthesis is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

8.1 Storage

The bioprosthesis must be stored between 10 °C-25 °C (50 °F-77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the bioprosthesis to extreme temperature.

The RetroFlex 3 delivery system should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3 Tesla.
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33 Ed. 3.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce a temperature rise of less than 1.1 °C above background for a whole body SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T cylindrical whole body MR system, assessed using a GE Signa whole body coil and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.2 W/kg and local background SAR at the site of the implant was 5.6 W/kg. The measured rise above background was 0.7 °C for a whole body SAR of 2 W/kg in a 3.0 T cylindrical bore whole body MR system, assessed using a GE Signa HDx whole body active shield MR scanner with software version 14/LX/MR and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.9 W/kg and local background SAR at the site of the implant was 8.4 W/kg.

The image artifact extended as far as 15 mm from the implant for spin echo images and 40 mm for gradient images when scanned in non-clinical testing in a 3.0 T GE Signa HDx MR system. The implant has not been evaluated in MR systems other than 1.5 or 3.0 T.

10.0 Patient Information

A patient implant card is provided in the patient information brochure and should be given to every patient after the procedure prior to discharge. The serial number and model number may be found on the package.

11.0 Recovered Clinical Bioprosthesis

The explanted bioprosthesis should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Disposal of Used Delivery Devices

Used delivery devices may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies

The Placement of Aortic Transcatheter Valves (PARTNER) trial, a prospective, randomized-controlled, multi-center pivotal trial, evaluated the safety and effectiveness of the Edwards SAPIEN Transcatheter Heart Valve via transfemoral and transapical delivery in a stratified population of high-risk and inoperable patients with severe symptomatic native aortic stenosis. Patients were stratified into two cohorts based on their risk of operability for standard aortic valve replacement surgery – those who were considered high surgical risk were eligible for Cohort A, while inoperable patients were eligible for Cohort B due to coexisting conditions that resulted in the probability of death or irreversible morbidity exceeding 50%.

Study Design – Cohort A

This was a randomized study with the primary objective of ascertaining if TAVR is non-inferior to AVR surgery with respect to 12-month survival outcomes in high-risk surgical patients. Other

objectives were focused on characterizing the benefit to risk ratio of TAVR relative to AVR.

Patients in Cohort A were first evaluated for vascular access to determine whether their peripheral arteries could accommodate the 22 or 24 French sheaths required for the transfemoral TAVR approach to deliver the 23 mm or 26 mm Edwards SAPIEN valve sizes. Those patients who could accommodate these sheaths were then randomized 1:1 between transfemoral TAVR and surgical AVR. Those patients whose arteries could not accommodate these sheaths were randomized 1:1 between transapical TAVR and surgical AVR.

The primary study endpoint was based on a pooled transapical and transfemoral analysis, and was defined as freedom from all-cause mortality at one year for the high-risk cohort. All patients were followed for at least 1 year, and cross-over from the surgical AVR group to the TAVR group was not permitted, except when findings or events during the assigned procedure prevented the planned treatment. Prespecified secondary endpoints included the following: time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within one year for which MACCE definition was comprised of death, MI, stroke, and renal failure as defined by protocol, total hospital days through one year, NYHA functional class at one year, and 6-minute walk test at one year. Additional prespecified efficacy endpoints were measured at 30 days, six months, and one year for the following: functional improvement from baseline as measured per (1) NYHA functional classification, (2) EOA, and (3) 6-minute walk test, freedom from MACCE, improved Quality of Life (QoL), and improved valve function demonstrated by an improvement in EOA.

Study Design – Cohort B

This was a randomized study with the primary objective of ascertaining if TAVR is superior to standard therapy in a control group for inoperable patients with respect to 12-month survival outcomes. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to the standard therapy control group.

Patients in Cohort B were also evaluated for vascular access and those meeting the criteria were randomized 1:1 to either transfemoral delivery of the Edwards SAPIEN valve or to a control group. Patients in the control group were treated with medication and/or balloon valvuloplasty. Patients in Cohort B who did not meet the criteria for vascular access were not eligible for the trial.

Study Results – Cohort A

A total of 699 (657 in the As-Treated [AT] population) high-risk patients with severe aortic stenosis were enrolled at 26 centers (23 in the United States) and assigned to TAVR (344 patients) or AVR (313 patients) with baseline characteristics described in Table 1. Among the TAVR patents, 240 were treated using transfemoral access and 104 were treated using transapical access. Severe aortic stenosis was defined as a mean gradient > 40 mmHg, jet velocity > 4.0 m per sec, or an initial aortic valve area (AVA) of 0.8 cm^2. The primary endpoint for the high-risk cohort was freedom from all-cause mortality at one year. Clinical outcomes of TAVR (transfemoral and transapical) as compared to AVR are summarized in Tables 5, 6, and 7. At day 365, the Kaplan-Meier estimate of all-cause death was 23.7% in the TAVR group, as compared to 25.2% in the AVR group. The estimated difference between these treatment groups is -1.5% with a one-sided lower 95% confidence interval of -4.0%, which is greater than the pre-specified margin of -7.5%. The non-inferiority p-value for this difference is 0.0037, indicating that TAVR is non-inferior to AVR with respect to all-cause death [Figure 3]. Pre-specified secondary endpoints included valve performance [Figures 6 and 7] and NYHA functional class [Figure 8]. When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR was more likely than AVR to reduce cardiac symptoms (New York Heart Association class ≤ II) (P<0.0030). At 1 year, both TAVR and AVR improved cardiac symptoms with no evidence of treatment differences. The majority of strokes were reported at ≤ 30 days; the rate was 4.4% in the TAVR arm and 2.6% in the AVR arm (P=0.2064). At one year, the rate of stroke was 5.8% in the TAVR arm and 3.0% in the AVR arm (P=0.0887). Hemorrhagic/vascular events occurred in 24.5% of TAVR patients as compared to 27.8% of AVR patients between 0 and 30 days (P=0.3332). Between 0 days and one year, hemorrhagic/vascular events occurred in 26.8% of TAVR patients as compared to 28.6% of AVR patients (P=0.6248). Bleeding events occurred in 10.2% of TAVR patients vs. 28.4% of AVR patients (P<0.0001) between 0 and 30 days and in 10.2% of TAVR patients vs. 28.4% of AVR patients between 0 and 365 days (P<0.0001). New-onset atrial fibrillation was seen in 8.7% of TAVR patients as compared to 18.2% of AVR patients (P=0.0005). Aortic valve gradients and areas improved significantly after TAVR and AVR at 30 days and 1 year. There were small differences in aortic valve gradients and areas favoring TAVR (at 1 year, mean gradient 10.2 vs. 11.4 mm Hg; P=0.0131 and valve area 1.59 vs. 1.44 cm^2; P=0.0027). Moderate or severe para-valvular regurgitation was more frequent after TAVR than AVR (at 30-days, 11.7% vs.

0.9%, respectively, with P<0.0001; at 1-year, 6.5% vs. 1.9%, respectively, with P<0.0469).

In patients with severe aortic stenosis who are at high-risk for operation, TAVR and AVR had similar survival after 1 year and similar improvement in cardiac symptoms. TAVR patients experienced a higher incidence of strokes and major vascular events. AVR patients experienced a higher incidence of bleeding. With respect to the transfemoral approach in both the ITT and AT populations, all cause mortality in the TAVR arm was non-inferior to all cause mortality in the AVR arm at 1 year. With respect to the transapical approach in both the ITT and AT populations, all cause mortality was not shown to be non-inferior to all cause mortality in the AVR arm at 1 year. The study was not powered for this analysis.

In conclusion, when used in the high surgical risk population the benefits and risks associated with TAVR are non-inferior to the risks and benefits associated with surgical AVR.

Study Results – Cohort B

A total of 358 patients (ITT population) with severe aortic stenosis were enrolled and underwent 1:1 randomization at 22 centers (18 in the United States) with baseline characteristics described in Table 2. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mmHg or more, or a peak aortic-jet velocity of 4.0 m per second or more. The primary end point was the rate of death from any cause over the duration of the trial. At 1 year, the rate of death from any cause (Kaplan-Meier analysis) was 30.7% with TAVR, as compared with 50.7% in the group not receiving the valve (hazard ratio with TAVR, 0.51; 95% confidence interval [CI], 0.39 to 0.68; P < 0.0001) (Figure 9). A total of 141 of the 179 (78.8%) patients in the control group underwent balloon aortic valvuloplasty (BAV). In addition, 11 patients (6.1%) underwent aortic valve replacement. 5 patients (2.8%) received an LV-descending aortic conduit, and 4 patients (2.2%) received a THV outside the US. The co-primary composite end point was time of death from any cause or the time to the first occurrence of repeat hospitalization. The rate of the composite end point of death from any cause or repeat hospitalization was 43.6% with TAVR as compared with 71.6% in the control group (hazard ratio, 0.45; 95% CI, 0.35 to 0.59; P < 0.0001) (Figure 10). Prespecified secondary end points included the rate of death from cardiovascular causes (Figure 11), NYHA functional class (Figure 14), valve performance (Figures 12 and 13), and the distance covered during a 6-minute walk test. Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVR than among those in the control group (23.9% vs. 60.8%, P < 0.001). When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR, as compared with the control, was associated with a higher incidence of strokes (7.3% vs. 1.7%, P = 0.02) and major vascular complications (16.8% vs. 1.1%, P < 0.0001). The time from index procedure to stroke in the TAVR group was as follows: 1 stroke at 12 days before the index procedure but after randomization, 4 strokes on the day of the index procedure, 2 strokes on the first post-operative day and 2 on the second post-operative day, and one stroke each on days 3, 5, 10, 23, 39, 51, 75, 120, 136, and 151. At 1 year, the rate of hemorrhagic vascular complication was 34.3% in the TAVR group, as compared to 17.7% in the control group. At 1 year, the rate of bleeding events was 17.3% in the TAVR group, as compared to 2.2% in the control group. Additionally, at 1 year, the rate of endocarditis was 1.4% in the TAVR group, as compared to 0.8% in the control group. Mean index hospital stay was 8.5 days for the TAVR group, as compared to 7.6 days for the control group. Mean days alive out of hospital was 273.8 days for the TAVR group and 210.2 days for the control group. At 1 year, the rate of aortic regurgitation for the TAVR group was as follows: 2% of patients at 4+, 13% of patients at 3+, 50% of patients at 2+, 20% of patients at 1+, and 11% of patients with no regurgitation. In comparison, the rate of aortic regurgitation of the control group was as follows: 17% of patients at 3+, 39% of patients at 2+, 37% of patients at 1+, and 7% of patients with no regurgitation.

Procedure data for the TAVR group is summarized in Table 4. Clinical outcomes of TAVR as compared with the control are summarized in Table 8. In the two years after TAVR, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram.

Additional data for the inoperable patient population in Cohort B has been collected, reviewed, and adjudicated; results are summarized in Table 8.

In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, as compared with the control, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of stroke and major vascular events.

Non-Randomized Continued Access (NRCA) – Cohort A

Once study enrollment in the randomized protocol for Cohort A had been completed, 1521 additional patients were treated and followed in a non-randomized continued access cohort. Non-randomized continued access allowed eligible subjects to be treated with TAVR without randomization.

The non-randomized as treated cohort comprises 1521 patients and consists of 822 NRCA transapical patients and 699 NRCA transfemoral patients. In order to compare the randomized cohort population to the non-randomized population, pertinent demographic and baseline characteristics were compared post hoc. Compared to the randomized TAVR patients, the age of NRCA patients was slightly higher and more NRCA patients were female. In addition, NRCA patients had a higher incidence of CAD, prior PCI, and prior BAV and lower incidence of pulmonary hypertension and frailty compared to the randomized TAVR patients. Comparison of the key demographic and baseline characteristics of the high risk randomized TAVR patients vs. the NRCA patients may be found in Table 9. Inclusion criteria for the non-randomized cohort were the same as inclusion criteria for the randomized cohort.

Clinical outcomes of the NRCA population as compared to the randomized population may be found in Table 11. The Kaplan-Meier estimate, at 30 days, of all-cause mortality in the pooled NRCA group was 5.9%; the Kaplan-Meier estimate, at Day 365, of all-cause mortality in the pooled NRCA group was 21.6%. The respective Transapical Kaplan-Meier estimates at 30 days and 365 days were 8.2% and 23.6%; the respective Transfemoral Kaplan-Meier estimates at 30 days and 365 days were 3.2% and 19.4 %.

The Kaplan-Meier rate of stroke in the NRCA Transapical group at 30 days was 2.0%, whereas the Kaplan-Meier rate of stroke in the NRCA Transfemoral group at 30 days was 4.4%. At day 365, the Kaplan-Meier rate of stroke was 3.7% and 5.7% for Transapical and Transfemoral, respectively. Death and stroke data from 1521 pooled non-randomized continued access patients are available [Table 11]. These outcomes are better than the results obtained in the randomized TAVR cohort at one year.

Table 1: COHORT A - Baseline Characteristics of the Patients and Echocardiographic Findings* (AT Population)							
	Transapical Approach		Transfemoral Approach		Pooled Approaches		
	AVR	TAVR	AVR	TAVR	AVR	TAVR	P Value
Characteristic	(N = 92)	(N = 104)	(N = 221)	(N = 240)	(N = 313)	(N = 344)	
Age — yr	83.4 ± 5.5	82.9 ± 7.0	84.8 ± 6.6	83.9 ± 6.8	84.4 ± 6.3	83.6 ± 6.8	0.12
Male sex — no. (%)	55 (59.8)	53 (51.0)	124 (56.1)	145 (60.4)	179 (57.2)	198 (57.6)	0.94
STS score†	12.01 ± 3.5	11.7 ± 3.6	11.5 ± 3.3	11.9 ± 3.2	11.7 ± 3.4	11.8 ± 3.3	0.65
NYHA class — no. (%):							
II	4/92 (4.3)	8/104 (7.7)	12/221 (5.4)	12/240 (5.0)	16/313 (5.1)	20/344 (5.8)	0.73
III or IV	88/92 (95.7)	96/104 (92.3)	209/221 (94.6)	228/240 (95.0)	297/313 (94.9)	324/344 (94.2)	>0.999
Coronary artery disease — no. (%)	76/92 (82.6)	77/104 (74.0)	165/221 (74.7)	181/240 (75.4)	241/313 (77.0)	258/344 (75.0)	0.58
Previous myocardial infarction — no./total no. (%)	34/92 (37.0)	28/104 (26.9)	56/218 (25.7)	64/239 (26.8)	90/310 (29.0)	92/343 (26.8)	0.54
Previous intervention — no./total no. (%)							
CABG	51/92 (55.4)	51/104 (49.0)	88/221 (39.8)	95/240 (39.6)	139/313 (44.4)	146/344 (42.4)	0.64
PCI	39/91 (42.9)	33/104 (31.7)	62/221 (28.1)	82/238 (34.5)	101/312 (32.4)	115/342 (33.6)	0.74
Balloon aortic valvuloplasty	10/92(10.9)	13/104(12.5)	22/221(10.0)	33/240(13.8)	32/313(10.2)	46/344(13.4)	0.2287
Cerebral vascular disease — no./total no. (%)	26/86 (30.2)	40/96 (41.7)	53/206 (25.7)	56/227 (24.7)	79/292 (27.1)	96/323 (29.7)	0.48
Peripheral vascular disease — no./total no. (%)	56/90 (62.2)	65/103 (63.1)	76/217 (35.0)	83/238 (34.9)	132/307 (43.0)	148/341 (43.4)	0.94
COPD — no./total no. (%):							
Any	41/92 (44.6)	46/104 (44.2)	97/221 (43.9)	104/240 (43.3)	138/313 (44.1)	150/344 (43.6)	0.94
Oxygen-dependent	7/92 (7.6)	11/104 (10.6)	16/221 (7.2)	21/240 (8.8)	23/313 (7.3)	32/344 (9.3)	0.90
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	9/92 (9.8)	7/103 (6.8)	11/221(5.0)	30/237 (12.7)	20/313 (6.4)	37/340 (10.9)	0.05
Atrial fibrillation — no./total no. (%)	17/33 (51.5)	31/58 (53.4)	51/121 (42.1)	49/138 (35.5)	68/154 (44.2)	80/196 (40.8)	0.59
Permanent pacemaker — no./total no. (%)	17/92 (18.5)	21/104 (20.2)	53/221 (24.0)	48/240 (20.0)	70/313 (22.4)	69/344 (20.1)	0.50
Pulmonary hypertension — no./total no. (%)	38/92 (41.3)	55/104 (52.9)	112/221 (50.7)	117/240 (48.8)	150/313 (47.9)	172/344 (50.0)	0.07
Extensively calcified aorta — no. (%)	1/92 (1.1)	2/104 (1.9)	1/221 (0.5)	0/240 (0.0)	2/313 (0.6)	2/344 (0.6)	>0.999
Deleterious effects of chest-wall irradiation — no. (%)	0/92 (0.0)	2/104 (1.9)	2/221 (0.9)	1/240 (0.4)	2/313 (0.6)	3/344 (0.9)	>0.999
Chest-wall deformity — no. (%)	1/92 (1.1)	0/104 (0.0)	0/221 (0.0)	0/240 (0.0)	1/313 (0.3)	0/344 (0.0)	0.48
Liver disease — no./total no. (%)	0/92 (0.0)	2/104 (1.9)	9/221 (4.1)	6/240 (2.5)	9/313 (2.9)	8/344 (2.3)	0.81

Echocardiographic findings							
Aortic-valve area — cm^2 (n, mean)	88, 0.7 ± 0.2	95, 0.7 ± 0.2	207, 0.6 ± 0.2	223, 0.7 ± 0.2	295, 0.6 ± 0.2	318 ,0.7 ± 0.2	0.28
Mean aortic-valve gradient — mmHg (n, mean)	90, 40.5 ± 12.9	97, 41.7 ± 13.9	210, 44.6 ± 14.8	229, 43.0 ± 14.8	300, 43.4 ± 14.3	326, 42.6 ± 14.5	0.49
Mean LVEF — (n, mean)	89, 53.5 ± 10.9	98, 53.6 ± 12.2	211, 53.3 ± 13.3	232, 52.2 ± 14.0	300, 53.3 ± 12.6	330, 52.6 ± 13.5	0.48
Moderate or severe mitral regurgitation — no./total no. (%)¶	19/89 (21.3)	19/99 (19.2)	44/208 (21.2)	46/230 (20.0)	63/297 (21.2)	65/329 (19.8)	0.69

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 2: COHORT B - Baseline Characteristics of the Patients and Echocardiographic Findings* (ITT Population)			
	TAVR	Control Group	P Value
Characteristic	(N = 179)	(N = 179)	
Age — yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex — no. (%)	82 (45.8)	84 (46.9)	0.92
STS score†	11.2 ± 5.8	11.9 ± 4.8	0.14
NYHA class — no. (%):			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease — no. (%)	121 (67.6)	133 (74.3)	0.20
Previous myocardial infarction — no./total no. (%)	33/177 (18.6)	47/179 (26.3)	0.10
Previous intervention — no./total no. (%)			
CABG	58/179 (32.4)	73/179 (40.8)	0.12
PCI	47/179 (26.3)	39/179 (21.8)	0.39
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease — no./total no. (%)	48/175 (27.4)	46/171 (26.9)	1.00
Peripheral vascular disease — no./total no. (%)	55/178 (30.9)	45/179 (25.1)	0.24
COPD — no. (%):			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	8/179 (4.5)	16/178 (9.0)	0.10
Atrial fibrillation — no./total no. (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker — no./total no. (%)	35/179 (19.6)	31/179 (17.3)	0.68
Pulmonary hypertension — no./total no. (%)	50/118 (42.4)	53/121 (43.8)	0.90
Extensively calcified aorta — no. (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation — no. (%)	16 (8.9)	15 (8.4)	1.00
Chest-wall deformity — no. (%)	15 (8.4)	9 (5.0)	0.29
Liver disease — no./total no. (%)	6/177 (3.4)	6/178 (3.4)	1.00
Echocardiographic findings			
Aortic-valve area — cm2	0.6 ± 0.2	0.6 ± 0.2	0.97
Mean aortic-valve gradient — mmHg	44.5 ± 15.7	43.0 ± 15.3	0.39
Mean LVEF — %	53.9 ± 13.1	51.1 ± 14.3	0.06
Moderate or severe mitral regurgitation — no./total no. (%)¶	38/171 (22.2)	38/165 (23.0)	0.90

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 3: COHORT A - Procedure Data (AT Population)			
	TA TAVR	**TF TAVR**	**Pooled AVR**
Variable	**Mean of % of patients (min-max)**		
Total time of procedure (min)	225 (93 - 595)	246 (84 - 624)	333 (70 - 750)
Skin to skin time (min)	114	142	230 (169 - 295)
Fluoroscopy time (min)	35	30	N/A
Volume of contrast (ml)	104	148	N/A
Use of CPB	8.8%	2.1%	100%
Use of general anesthesia	100%	100%	100%
# of devices used			
0	2.9%	4.6%	N/A
1	89.2%	90.8%	100%
2	6.9%	4.2%	N/A
3	1.0%	0.4%	N/A
Valve in valve procedure	1.0%	0.4%	N/A
Emergent operation due to device or procedure	1.0%	1.3%	3.8%
Valve Size			
19 mm	N/A	N/A	11.9%
21 mm	N/A	N/A	39.7%
22 mm	N/A	N/A	0.3%
23 mm	51.5%	46.8%	34.9%
25 mm	N/A	N/A	11.9%
26 mm	48.5%	53.3%	N/A
27 mm	N/A	N/A	1.0%
29 mm	N/A	N/A	0.3%
Adverse event during procedure	19.6%	21.3%	14.7%
Device malfunction	2.0%	1.3%	N/A
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	84.5%	80.4%	N/A
Procedure Success (Device success, no MACCE < 30d)	75.3%	76.0%	N/A

Table 4: COHORT B - TAVR Procedure Data	
Variable	**Mean or % of patients (min – max)**
Total time of procedure (min)	262 (139-616)
Skin to skin time (min)	150 (34 – 553)
Fluoroscopy time (min)	29 (10-68)
Volume of contrast (ml)	132 (10-450)
Use of CPB	1.1%
Use of general anesthesia	100%
# of devices used 0 1 2 3	 4.6% 89.1% 5.7% 0.6%
Valve in Valve procedure	2.3%
Emergent operation due to device or procedure	1.1%
Valve Size 23 mm 26 mm	 56.6% 43.4%
Adverse event during procedure	39.4%
Device malfunction	3.4%
Device Success (deployment, AVA >0.9, AI<3+, 1 valve)	78.2%
Procedure Success (Device success, no MACCE <30d)	71.8%

Table 5: COHORT A - Clinical Outcomes of the Pooled TAVR and Pooled AVR Groups up to 2 Years (AT Population)												
	30 Days				31 Days - 1 Year				1 Year - 2 Years			
Outcome	Pooled TAVR N=344	KM Event rate TAVR*	Pooled AVR N=313	KM Event rate AVR	Pooled TAVR N=344	KM Event rate TAVR*	Pooled AVR N=313	KM Event rate AVR	Pooled TAVR N=344	KM Event rate TAVR*	Pooled AVR N=313	KM Event rate AVR
Death	18	5.2%	25	8.0%	63	23.7%	53	25.2%	33	33.9%	21	32.7%
Death from cardiovascular cause[a]	14	4.1%	9	2.9%	30	13.6%	24	11.5%	20	20.8%	16	18.5%
Repeat hospitalization[b]	18	5.4%	18	6.1%	40	17.3%	29	16.6%	15	23.8%	9	20.8%
Death from any cause or repeat hospitalization[b]	35	10.2%	43	13.8%	86	33.9%	74	35.5%	48	46.2%	33	44.4%
TIA[d]	3	0.9%	1	0.3%	5	2.7%	3	1.5%	2	3.6%	2	2.7%
All Stroke[c]	15	4.4%	8	2.6%	4	5.8%	1	3.0%	4	7.5%	3	4.4%
Myocardial Infarction[g]												
All	0	0.0%	1	0.3%	0	0.0%	0	0.3%	2	0.0%	0	1.3%
Peri-procedural	0	0.0%	1	0.3%	0	0.0%	0	0.3%	0	0.0%	0	0.3%
Hemorrhagic Vascular Complication[f]	84	24.5%	87	27.8%	10	26.8%	3	28.6%	3	28.0%	2	29.4%
Major Vascular Complication[i]	38	11.1%	12	3.8%	0	11.1%	0	3.8%	1	11.4%	0	3.8%
Renal Failure[h]	13	3.8%	14	4.6%	4	5.2%	5	6.5%	2	6.0%	0	6.5%
Renal Insufficiency	19	5.6%	18	5.8%	3	6.6%	7	7.8%	4	8.1%	1	8.3%
Bleeding Event[e]	35	10.2%	89	28.4%	0	10.2%	0	28.4%	0	10.2%	0	28.4%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	7	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	1	0.3%	3	1.0%	2	1.1%	1	1.5%	0	1.1%
New Atrial Fibrillation[j]	30	N/A	57	N/A	14	N/A	3	N/A	N/A	N/A	N/A	N/A
New pacemaker	16	4.7%	14	4.6%	4	6.1%	2	5.3%	2	6.9%	3	6.8%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 6: COHORT A - Clinical Outcomes in the Transfemoral Group up to 2 Years (AT Population)

	30 Days				31 Days - 1 Year				1 Year – 2 Years			
Outcome	TF TAVR N=240	KM Event rate TAVR*	AVR N=221	KM Event rate AVR	TF TAVR N=240	KM Event rate TAVR*	AVR N=221	KM Event rate AVR	TF TAVR N=240	KM Event rate TAVR*	AVR N=221	KM Event rate AVR
Death	9	3.7%	18	8.2%	42	21.4%	37	25.2%	21	30.7%	13	31.6%
Death from cardiovascular cause[a]	8	3.3%	7	3.2%	19	12.0%	17	11.8%	14	19.0%	9	17.3%
Repeat hospitalization[b]	13	5.5%	12	5.8%	29	17.6%	22	17.3%	8	22.4%	4	19.8%
Death from any cause or repeat hospitalization[b]	21	8.7%	30	13.6%	59	31.8%	52	35.3%	31	42.2%	18	42.2%
TIA[d]	3	1.3%	0	0.0%	2	2.3%	1	0.6%	1	2.8%	1	1.4%
All Stroke[c]	8	3.3%	3	1.4%	1	3.8%	0	1.4%	2	5.0%	1	2.0%
Myocardial Infarction[g]												
All	0	0.0%	1	0.5%	0	0.0%	0	0.5%	1	0.0%	0	1.1%
Peri-procedural	0	0.0%	1	0.5%	0	0.0%	0	0.5%	0	0.0%	0	0.5%
Hemorrhagic Vascular Complication[f]	69	28.8%	61	27.6%	5	30.2%	2	28.7%	1	30.7%	2	29.8%
Major Vascular Complication[i]	34	14.2%	7	3.2%	0	14.2%	0	3.2%	1	14.7%	0	3.2%
Renal Failure[h]	8	3.4%	7	3.2%	3	4.7%	4	5.5%	2	5.8%	0	5.5%
Renal Insufficiency	7	2.9%	13	6.0%	2	3.9%	6	8.2%	4	5.9%	0	8.2%
Bleeding Event[e]	27	11.3%	63	28.5%	0	11.3%	0	28.5%	0	11.3%	0	28.5%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	4	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	0	0.0%	2	1.0%	2	1.1%	1	1.6%	0	1.1%
New Atrial Fibrillation[j]	19	N/A	42	N/A	11	N/A	2	N/A	N/A	N/A	N/A	N/A
New pacemaker	11	4.6%	9	4.2%	3	6.0%	0	4.2%	2	7.2%	3	6.2%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR). c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 7: COHORT A - Clinical Outcomes in the Transapical Group up to 2 Years (AT Population)

	30 Days				31 Days - 1 Year				1 Year – 2 Years			
Outcome	TA TAVR N=104	KM Event rate TAVR*	AVR N=92	KM Event rate AVR	TA TAVR N=104	KM Event rate TAVR*	AVR N=92	KM Event rate AVR	TA TAVR N=104	KM Event rate TAVR*	AVR N=92	KM Event rate AVR
Death	9	8.7%	7	7.6%	21	29.1%	16	25.3%	12	41.3%	8	35.5%
Death from cardiovascular cause[a]	6	5.8%	2	2.2%	11	17.4%	7	10.8%	6	25.2%	7	21.6%
Repeat hospitalization[b]	5	5.1%	6	6.8%	11	16.7%	7	14.9%	7	27.4%	5	23.3%
Death from any cause or repeat hospitalization[b]	14	13.5%	13	14.1%	27	38.7%	22	36.3%	17	55.3%	15	49.6%
TIAd[d]	0	0.0%	1	1.1%	3	3.7%	2	3.9%	1	5.8%	1	5.6%
All Stroke[c]	7	7.0%	5	5.5%	3	10.8%	1	7.0%	2	13.8%	2	10.0%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.0%	0	15.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Hemorrhagic Vascular Complication[f]	15	14.5%	26	28.3%	5	19.2%	1	28.3%	2	22.0%	0	28.3%
Major Vascular Complication[i]	4	3.9%	5	5.4%	0	3.9%	0	5.4%	0	3.9%	0	5.4%
Renal Failure[h]	5	5.0%	7	7.7%	1	6.2%	1	8.9%	0	6.2%	0	8.9%
Renal Insufficiency	12	11.9%	5	5.5%	1	13.1%	1	6.9%	0	13.1%	1	8.4%
Bleeding Event[e]	8	7.7%	26	28.3%	0	7.7%	0	28.3%	0	7.7%	0	
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	3	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Endocarditis	0	0.0%	1	1.1%	1	1.2%	0	1.1%	0	1.2%	0	1.1%
New Atrial Fibrillation[j]	11	N/A	15	N/A	3	N/A	1	N/A				
New pacemaker	5	5.0%	5	5.6%	1	6.2%	2	8.1%	0	6.2%	0	8.1%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patient unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
j. New atrial fibrillation as defined by ECG corelab.

Table 8: Cohort B - Clinical Outcomes up to 2 Years (ITT Population)

	30 Days				31 Days - 1 Year				1 Year - 2 Years			
Outcome	TAVR N=179	KM Event rate*	Control Group N=179	KM Event rate	TAVR N=179	KM Event rate*	Control Group N=179	KM Event rate	TAVR N=179	KM Event rate*	Control Group N=179	KM Event rate
Death from any cause	9	5.0%	5	2.8%	46	30.7%	84	50.7%	22	43.3%	28	68.0%
Death from cardiovascular cause[a]	8	4.5%	3	1.7%	27	20.5%	72	44.6%	15	31.0%	25	62.4%
Repeat hospitalization[b]	12	6.9%	18	10.2%	35	27.0%	70	53.9%	15	35.0%	24	72.5%
Death from any cause or repeat hospitalization[b]	21	11.7%	22	12.3%	62	44.1%	117	71.6%	31	56.7%	45	87.9%
TIA[d]	0	0.0%	0	0.0%	1	0.7%	0	0.0%	2	2.5%	0	0.0%
All Stroke[c]	13	7.3%	3	1.7%	6	11.2%	5	5.5%	3	13.8%	0	5.5%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	1	0.8%	1	0.7%	1	1.6%	1	2.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Hemorrhagic Vascular Complication[f]	46	25.8%	10	5.7%	16	34.3%	16	17.7%	8	39.8%	5	22.9%
Major Vascular Complication[i]	30	16.8%	2	1.1%	2	17.4%	2	2.8%	0	17.4%	0	2.8%
Renal Failure[h]	2	1.1%	3	1.7%	2	2.3%	4	4.7%	1	3.2%	3	7.6%
Renal Insufficiency	8	4.6%	1	0.6%	4	7.3%	5	4.2%	3	9.9%	4	9.6%
Bleeding Events[e]	29	16.2%	4	2.2%	2	17.3%	0	2.2%	0	17.3%	0	2.2%
Cardiac reintervention												
Balloon aortic valvuloplasty	3	1.7%	11	6.1%	0	1.7%	41	29.1%	2	3.4%	7	33.0%
Repeat TAVR[e]	3	N/A	N/A	N/A	0	N/A	N/A	N/A	0	N/A	N/A	N/A
Aortic-valve replacement	0	0.0%	4	2.3%	0	0.0%	6	7.6%	1	0.9%	1	8.9%
Endocarditis	0	0.0%	0	0.0%	2	1.4%	1	0.8%	1	2.3%	0	0.8%
New Atrial Fibrillation[j]	13	N/A	13	N/A	3	N/A	8	N/A	N/A	N/A	N/A	N/A
New pacemaker	6	3.4%	9	5.1%	2	4.7%	5	8.6%	2	6.4%	0	8.6%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.

N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patient unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).

c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.

e. Bleeding event is defined as ≥ 2 units within the index procedure.

f. Hemorrhagic vascular complications are defined as a hematoma at the access site >5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index

Table 8: Cohort B - Clinical Outcomes up to 2 Years (ITT Population)

procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non -Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).

i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

j. New atrial fibrillation as defined by ECG corelab.

Table 9: NRCA (Cohort A) - Baseline Characteristics of the Patients and Echocardiographic Findings* (AT Population)			
Characteristic	Pooled (N=1521)	TA (N=822)	TF (N=699)
Age - years	85.5 ± 6.3	84.7 ± 6.3	86.3 ± 6.2
Male sex - no./total no. (%)	777/1519 (51.2%)	383/822 (46.6%)	394/697 (56.5%)
STS score	11.8 ± 3.8	12.2 ± 4.5	11.3 ± 2.8
Logistic EuroSCORE	28.4 ± 47.7	28.4 ± 16.6	28.5 ± 68.5
NYHA class - no./total no. (%)	1518/1518 (100.0%)	822/822 (100.0%)	696/696 (100.0%)
II	70/1518 (4.6%)	43/822 (5.2%)	27/696 (3.9%)
III	724/1518 (47.7%)	411/822 (50.0%)	313/696 (45.0%)
IV	722/1518 (47.6%)	368/822 (44.8%)	354/696 (50.9%)
Coronary artery disease - no./total no. (%)	1213/1518 (79.9%)	690/821 (84.0%)	523/697 (75.0%)
Previous MI - no./total no. (%)	399/1511 (26.4%)	236/819 (28.8%)	163/692 (23.6%)
Prior CABG - no./total no. (%)	670/1519 (44.1%)	416/822 (50.6%)	254/697 (36.4%)
Prior PCI - no./total no. (%)	665/1518 (43.8%)	391/821 (47.6%)	274/697 (39.3%)
Prior BAV - no./total no. (%)	400/1509 (26.5%)	242/818 (29.6%)	158/691 (22.9%)
Peripheral vascular disease - no./total no. (%)	694/1502 (46.2%)	495/813 (60.9%)	199/689 (28.9%)
Cerebral vascular disease - no./total no. (%)	400/1499 (26.7%)	248/812 (30.5%)	152/687 (22.1%)
COPD - no./total no. (%)			
Any	657/1521 (43.2%)	371/822 (45.1%)	286/699 (40.9%)
Oxygen dependent	174/904 (19.2%)	89/507 (17.6%)	85/397 (21.4%)
Creatinine > 2mg/dL - no./total no. (%)	139/1503 (9.2%)	73/815 (9.0%)	66/688 (9.6%)
Atrial fibrillation - no./total no. (%)	120/279 (43.0%)	56/133 (42.1%)	64/146 (43.8%)
Permanent pacemaker - no./total no. (%)	345/1517 (22.7%)	178/820 (21.7%)	167/697 (24.0%)
Pulmonary hypertension - no./total no. (%)	553/1514 (36.5%)	291/819 (35.5%)	262/695 (37.7%)
Frailty - no./total no. (%)	157/1515 (10.4%)	83/819 (10.1%)	74/696 (10.6%)
Extensively calcified aorta - no./total no. (%)	16/1515 (1.1%)	13/819 (1.6%)	3/696 (0.4%)
Deleterious effects of chest-wall irradiation - no./total no. (%)	6/1515 (0.4%)	3/819 (0.4%)	3/696 (0.4%)
Chest-wall deformity - no./total no. (%)	7/1515 (0.5%)	3/819 (0.4%)	4/696 (0.6%)
Liver disease - no./total no. (%)	37/1516 (2.4%)	22/820 (2.7%)	15/696 (2.2%)
Echocardiographic Findings			
Aortic valve area - cm^2	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2
Mean aortic valve gradient - mm Hg	44.6 ± 15.0	44.0 ± 15.1	45.2 ± 14.9
Mean LVEF - %	53.0 ± 13.0	53.3 ± 12.8	52.6 ± 13.3
Moderate or severe MR - no./total no. (%)	144/640 (22.5%)	72/335 (21.5%)	72/305 (23.6%)

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.
¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 10: NRCA (Cohort A) Procedure Data (AT Population)		
	TA NRCA	TF NRCA
Variable		
Total time of procedure (min)	235.51	219.34
Skin to skin time (min)	121.78	114.37
Fluoroscopy time (min)	14.75	25.16
Volume of contrast (ml)	101.35	139.78
Use of CPB	10.4%	1.4%
Use of general anesthesia	99.9%	99.9%
# of devices used		
0	8.8%	9.9%
1	87.2%	85.3%
2	3.6%	4.6%
3	0.4%	0.3%
Valve in valve procedure	2.1%	2.1%
Valve Size		
19 mm	N/A	N/A
21 mm	N/A	N/A
22 mm	N/A	N/A
23 mm	53.4%	52.5%
25 mm	N/A	N/A
26 mm	46.6%	47.3%
27 mm	N/A	N/A
29 mm	N/A	1 (0.1%)
Adverse event during procedure	17.6%	23.1%
Device malfunction	0.5%	0.6%
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	39.8%	39.1%
Procedure Success (Device success, no MACCE < 30d)	38.0%	36.9%

Table 11: Randomized v. Nonrandomized (Cohort A) - Clinical Outcomes up to 1 Year (AT Population)

	0 -30 Days										31 Days - 1 Year									
	PMA Pooled		PMA TA		PMA TF		Transfemoral Approach NRCA TF		Transapical Approach NRCA TA		PMA Pooled		PMA TA		PMA TF		Transfemoral Approach NRCA TF		Transapical Approach NRCA TA	
Outcome (NRCA)	Pooled	KM Pooled	TA	KM TA	TF	KM TF	TF	KM Event rate TF	TA	KM Event rate TA	Pooled	KM Pooled	TA	KM TA	TF	KM TF	TF	KM Event rate TF	TA	KM Event rate TA
Death	18	5.2%	9	8.7%	9	3.7%	22	3.2%	66	8.2%	63	23.7%	21	29.1%	42	21.4%	74	19.4%	82	23.6%
Death from cardiovascular cause[a]	14	4.1%	6	5.8%	8	3.3%	16	2.3%	46	5.7%	30	13.6%	11	17.4%	19	12.0%	51	14.2%	48	15.3%
Death from any cause or repeat hospitalization[b]	35	10.2%	14	13.5%	21	8.7%	41	6.0%	86	10.8%	86	33.9%	27	38.7%	59	31.8%	99	25.8%	115	30.7%
All Stroke[c]	15	4.4%	7	7.0%	8	3.3%	30	4.4%	16	2.0%	4	5.8%	3	10.8%	1	3.8%	6	5.7%	6	3.7%

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

Figures – Cohort A

Figure 3. COHORT A - Primary Endpoint
All Cause Mortality (AT Population)
(68% confidence limits displayed)

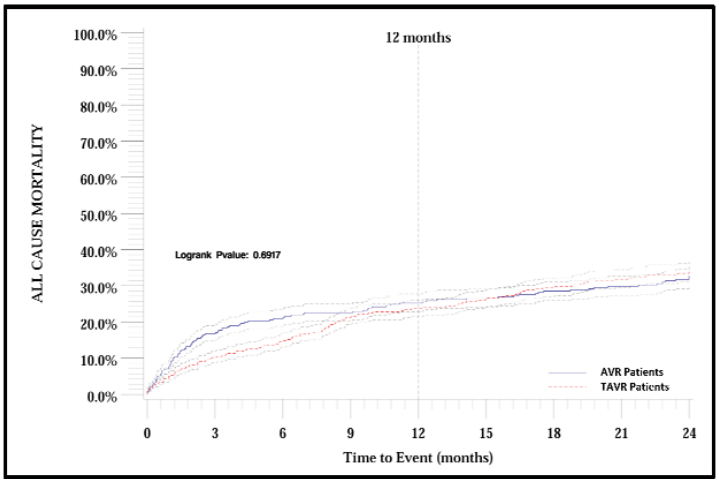


Figure 4. COHORT A - Secondary Endpoint
Mortality or Repeat Hospitalization (AT Population)
(68% confidence limits displayed)

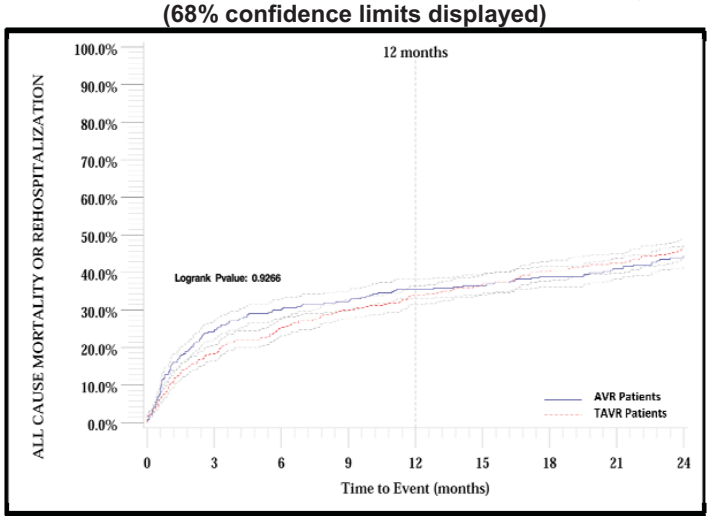


Figure 5. COHORT A – Secondary Endpoint:
Death from Cardiovascular Cause (AT Population)
(68% confidence limits displayed)

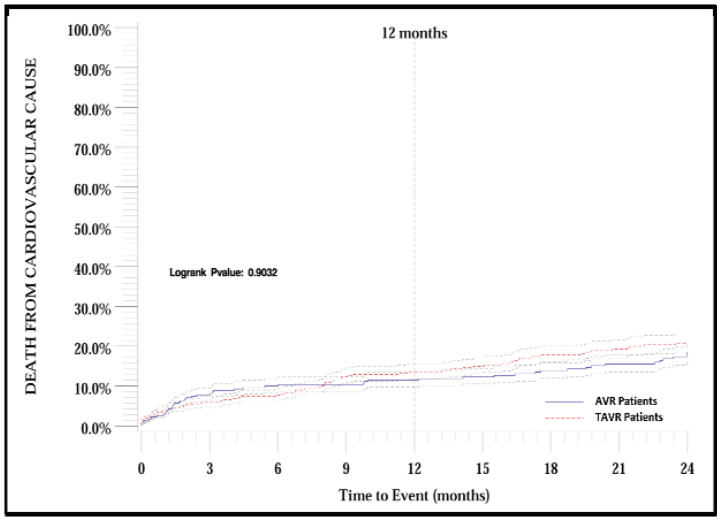


Figure 6. COHORT A - Secondary Endpoint:
AVA Over Time (AT Population)
(one standard deviation displayed)

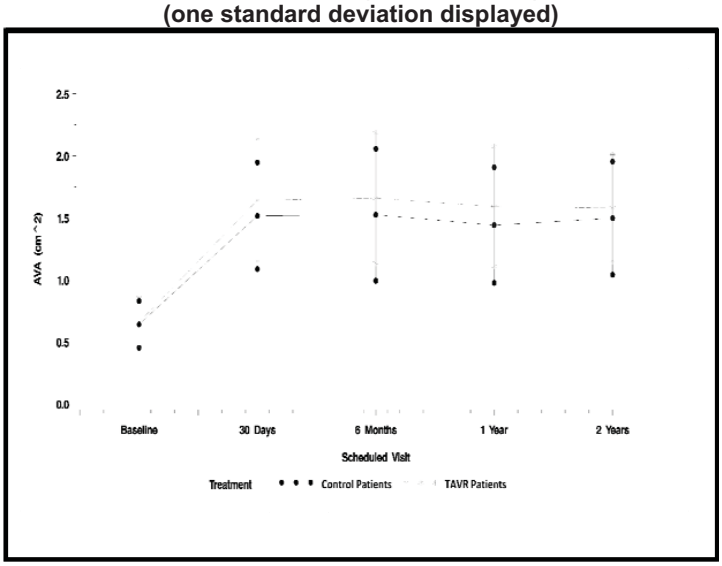


**Figure 7. COHORT A - Secondary Endpoint:
Mean Gradient Over Time (AT Population)
(one standard deviation displayed)**

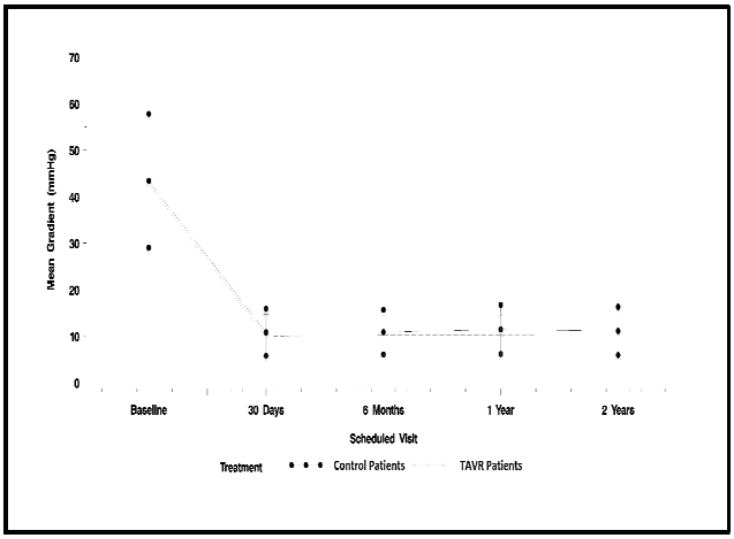
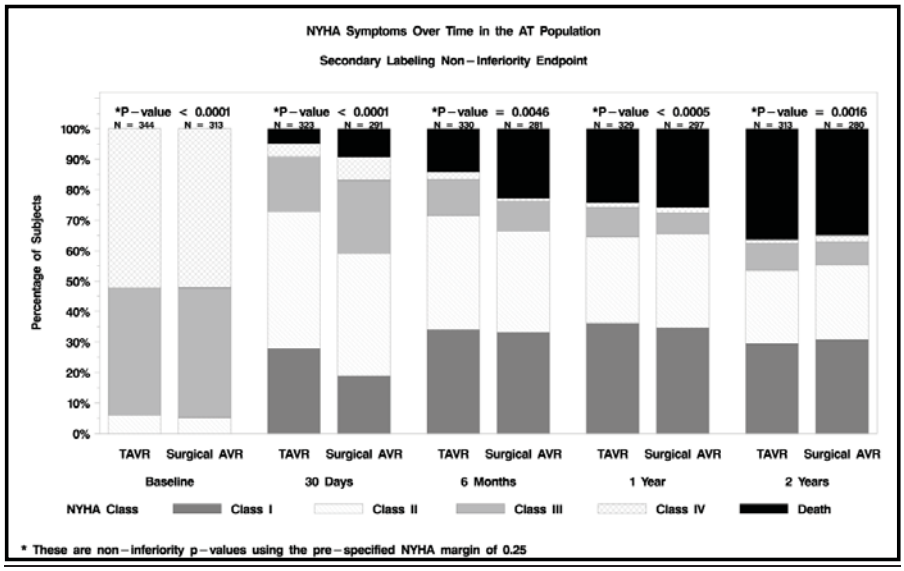


**Figure 8. COHORT A- Secondary Endpoint:
NYHA at 2 Year Visit (AT Population)**



Figures – Cohort B

Figure 9. COHORT B - Primary Endpoint
All Cause Mortality (ITT Population)
(68% confidence limits displayed)

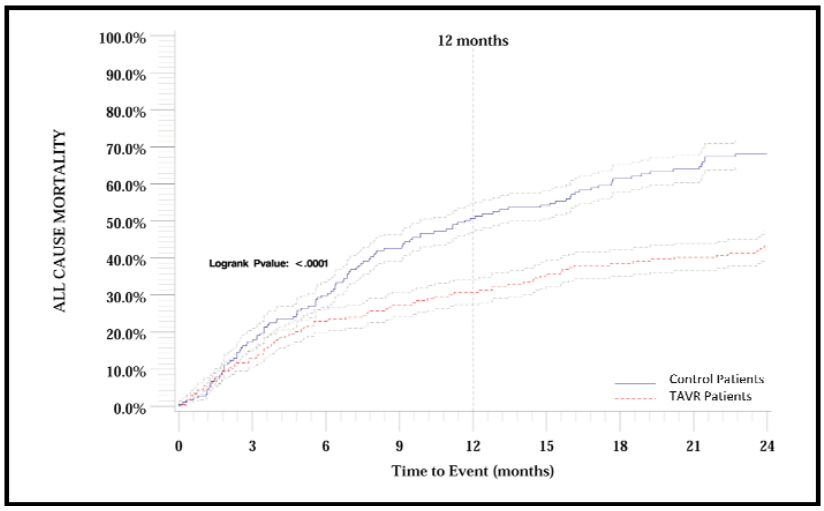


Figure 10. COHORT B - Co-Primary Endpoint
Mortality or Repeat Hospitalization (ITT Population)
(68% confidence limits displayed)

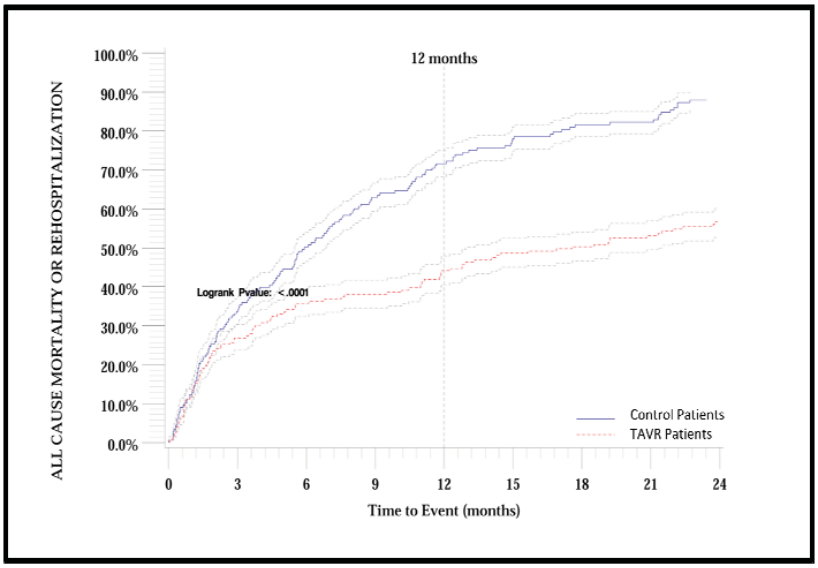


Figure 11. COHORT B – Secondary Endpoint
Death from Cardiovascular Cause (ITT Population)
(68% confidence limits displayed)

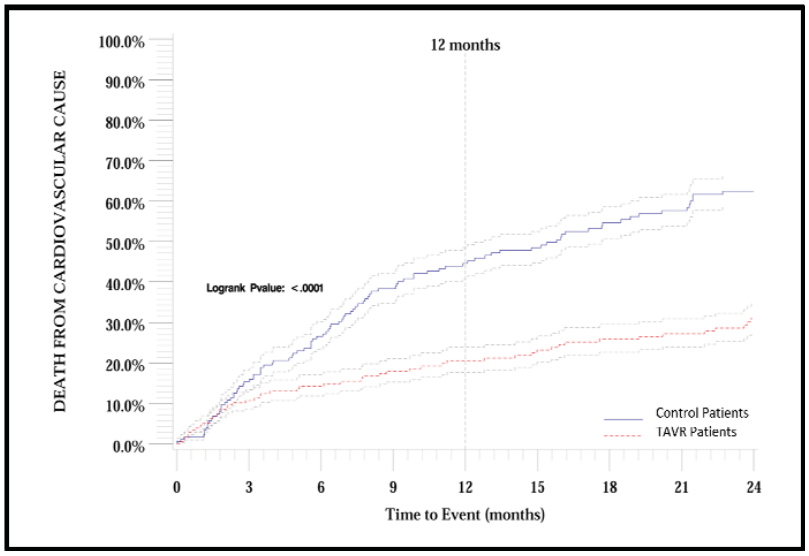


Figure 12. COHORT B - Secondary Endpoint:
AVA Over Time (ITT Population)
(one standard deviation displayed)

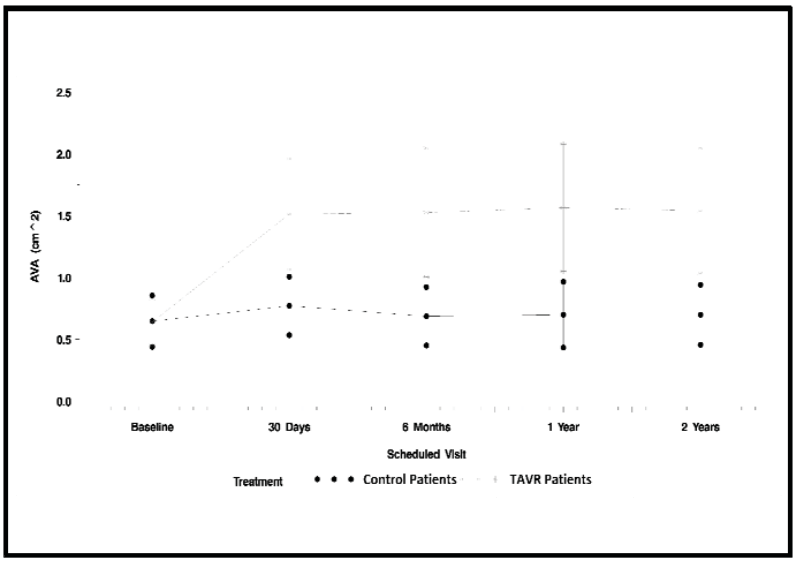


**Figure 13. COHORT B- Secondary Endpoint:
Mean Gradient Over Time (ITT Population)
(one standard deviation displayed)**

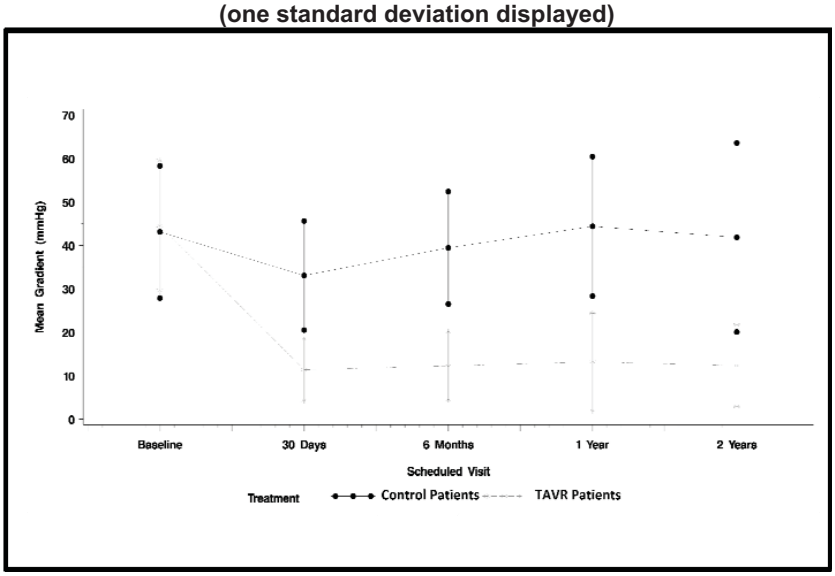
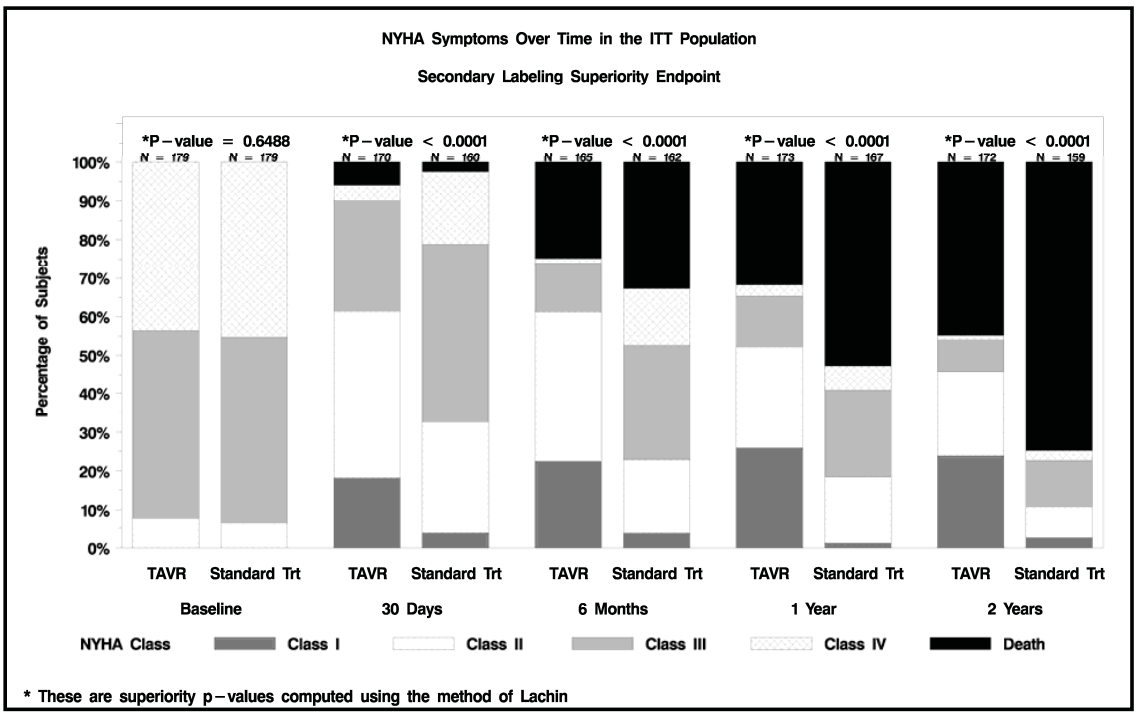


**Figure 14. COHORT B- Secondary Endpoint:
NYHA at 2 Year Visit (ITT Population)**



Figures – Cohort A Non Randomized Continued Access (NRCA)

Figure 15. All Cause Mortality:
Comparison of NRCA Patients to Pooled Randomized Patients (AT Population)
(68% confidence limits displayed)

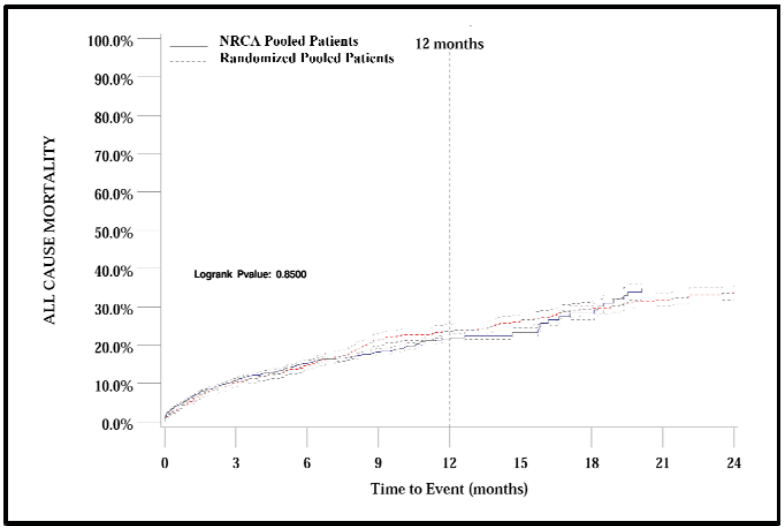


Figure 16. Stroke:
Comparison of NRCA Patients to Pooled Randomized Patients (AT Population)
(68% confidence limits displayed)

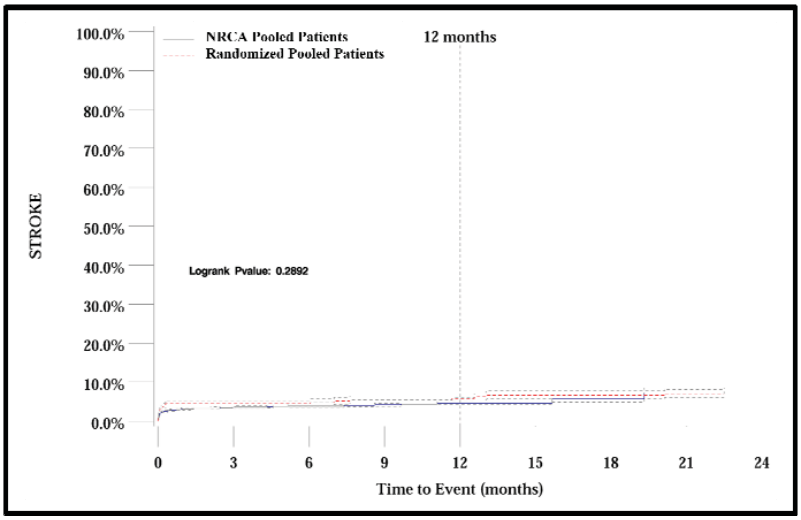


Figure 17. All Cause Mortality:
Comparison of NRCA Patients to Randomized TF Patients (AT Population)
(68% confidence limits displayed)

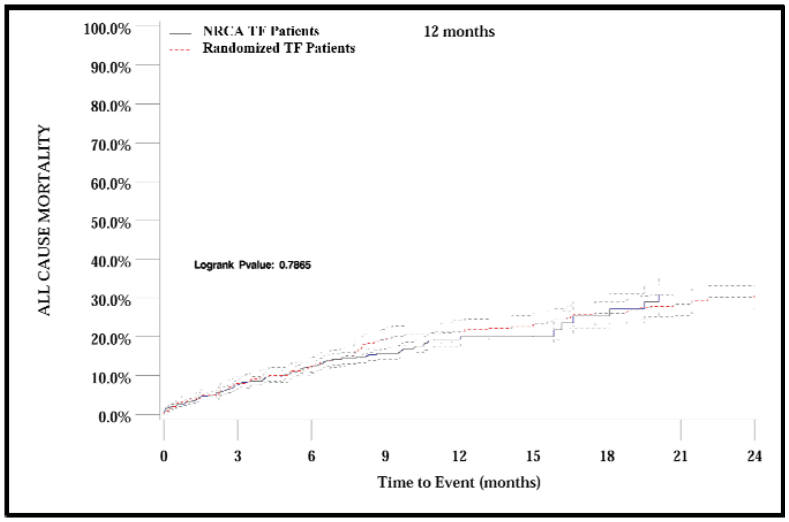


Figure 18. Stroke:
Comparison of NRCA Patients to Randomized TF Patients (AT Population)
(68% confidence limits displayed)

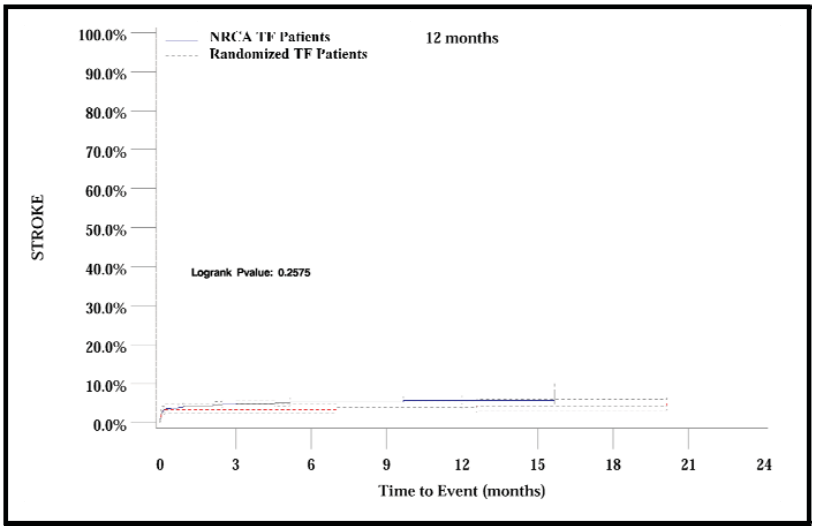


Figure 19. All Cause Mortality:
Comparison of NRCA Patients to Randomized TA Patients (AT Population)
(68% confidence limits displayed)

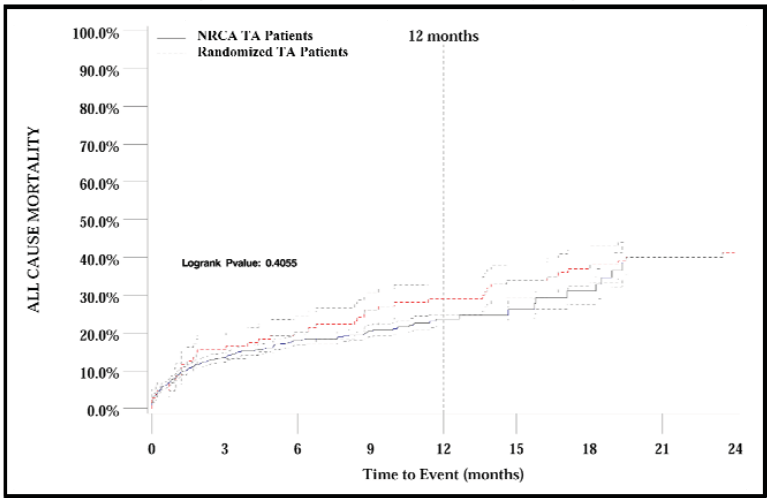
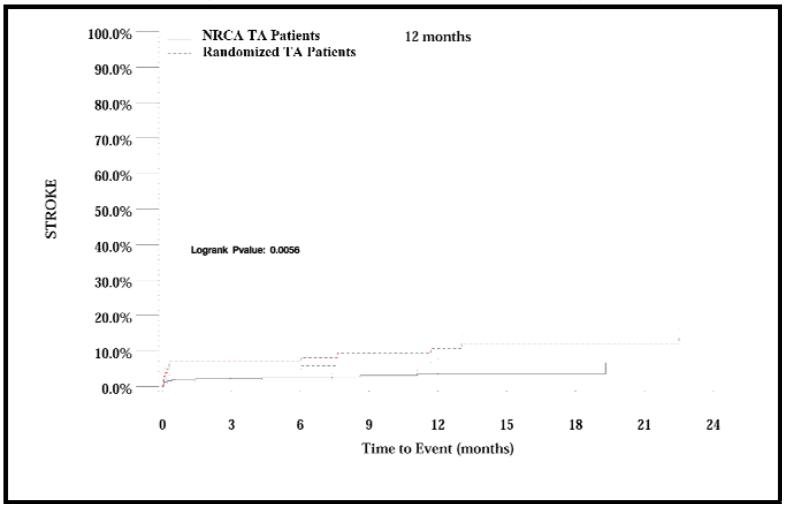


Figure 20. Stroke:
Comparison of NRCA Patients to Randomized TA Patients (AT Population)
(68% confidence limits displayed)



RetroFlex Balloon Catheter

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

STERILE: The balloon catheter is supplied sterilized by ethylene oxide.

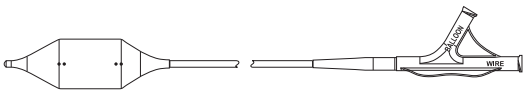
1.0 Device Description

The RetroFlex Balloon Catheter consists of a shaft and balloon with radiopaque markers indicating working length of the balloon. At the proximal end of the device, there is a standard "Y-connector" for balloon inflation and the guidewire lumen. The inflation parameters are as follows:

Table 1. Inflation Parameters

Model	Balloon Dimensions	Inflation Volume
9120BC20	20 mm x 3 cm	13 mL
9120BC23	23 mm x 3 cm	16 mL

RetroFlex Balloon Catheter THV114



Black dots indicate position of radiopaque markers.

Edwards Lifesciences, the stylized E logo, Edwards, and RetroFlex are trademarks of Edwards Lifesciences Corporation.

Device Compatibility:

- Maximum guidewire diameter: 0.035" (0.89 mm)
- Minimum sheath compatibility: 14F (4.62 mm)

NOTE: For proper volume sizing, the balloon catheter should be used with the inflation device provided by Edwards Lifesciences.

2.0 Indications

The RetroFlex balloon catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of a transcatheter heart valve.

3.0 Contraindications

- Other than standard risks associated with insertion of a cardiovascular catheter, there are no known contraindications for valvuloplasty. The patient's medical condition could affect successful use of this catheter.

4.0 Warnings

- The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not mishandle the device or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.

5.0 Precautions

- For special considerations associated with the use of this device prior to transcatheter heart valve implantation, refer to the bioprosthesis Instructions for Use.
- Use only appropriate balloon inflation medium. Do not use air or gaseous medium to inflate the balloon.
- The device is not intended for post-dilatation of deployed transcatheter heart valves.
- While exposed within the body, device advancement and retrieval should not be done without the aid of fluoroscopy. Do not advance or retract the device unless the balloon is fully deflated under vacuum.

6.0 Potential Adverse Events

Complications associated with standard catheterization, balloon valvuloplasty, and the use of angiography include, but are not limited to, allergic reaction to anesthesia or to contrast media, injury including perforation or dissection of vessels, thrombus formation, plaque dislodgement and embolization that may result in myocardial infarction, stroke, distal peripheral occlusion and/or death, arrhythmia development, cardiac perforation, conduction system injury, hematoma, infundibulum injury, annular tear or rupture and/or valve leaflet dehiscence, severe valve insufficiency, valve restenosis, valve damage, balloon rupture.

7.0 Directions for Use

Step	Procedure
1	Prepare vascular access site for valvuloplasty balloon catheter insertion and position guidewire using standard techniques.
2	Flush the valvuloplasty balloon catheter with heparinized saline. Attach a high pressure 3-way stopcock to the balloon inflation port.
3	Prepare a 20 mL syringe with 5 mL diluted contrast solution (15:85 contrast to heparinized saline) and attach to the stopcock.
4	Completely fill the inflation device provided by Edwards with diluted contrast solution and attach in the locked position to the stopcock; close the stopcock to the inflation device.
5	Slowly pull vacuum with the 20 mL syringe repeatedly to remove air, leaving neutral pressure in the system.
6	Close the stopcock to the balloon catheter. Gradually remove contrast medium into the 20 mL syringe to achieve the appropriate volume by rotating the knob of the inflation device. Close the stopcock to the 20 mL syringe and remove the 20 mL syringe from the system.
7	Remove balloon cover and hydrate the length of the balloon catheter.
8	Advance the balloon catheter over the guidewire, through the introducer sheath, across the valve, and position the balloon markers at the intended site.
9	Fully inflate the balloon with the inflation device.
10	Completely deflate the balloon, and gently withdraw the valvuloplasty balloon catheter and remove from the sheath.

8.0 How Supplied

STERILE: The balloon catheter is supplied sterilized by ethylene oxide.

9.0 Storage

Store in a cool, dry place.

10.0 Device Disposal

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

Edwards

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Irvine, CA 92614-5686 USA
Made in USA

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Web IFU
155422001 A

Crimper
Model 9100CR23/ 9100CR26

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

STERILE: The Crimper is supplied sterilized by ethylene oxide.

1.0 Device Description

The Crimper is comprised of a housing and a compression mechanism, creating an aperture that is opened and closed by means of a handle. The Crimper includes a balloon gauge to verify diameter of an inflated balloon catheter. The Crimper is available in two sizes, 23 mm and 26 mm, with a corresponding balloon gauge for each size. It also includes a crimp gauge to verify collapsed diameter of the device.

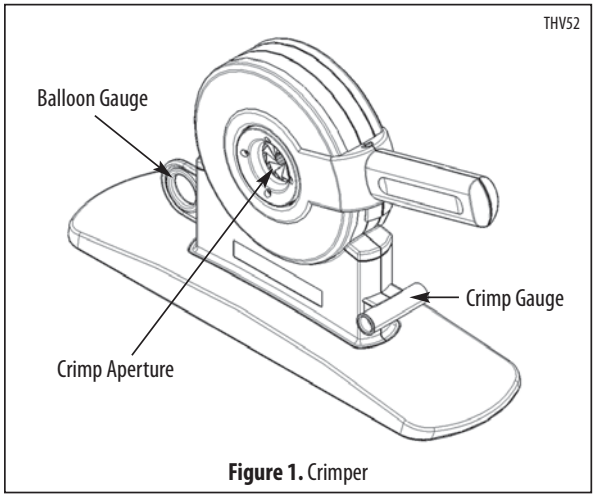

Figure 1. Crimper

2.0 Indications

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

3.0 Contraindications

No known contraindications.

4.0 Warnings

- The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not mishandle the device or use it if the packaging or any components are not sterile, have been opened or are damaged, or the expiration date has elapsed.

5.0 Precautions

For special considerations associated with the use of this device prior to transcatheter heart valve implantation, refer to the bioprosthesis Instructions for Use.

6.0 Potential Adverse Events

No known potential adverse events.

7.0 Directions for Use

1. Remove the bioprosthesis from its package and gently place the bioprosthesis into the crimper aperture.
2. Crimp the bioprosthesis by rotating the handle to close the aperture.

8.0 How Supplied

STERILE: The Crimper is supplied sterilized by ethylene oxide.

9.0 Storage

The Crimper should be stored in a cool, dry place.

10.0 Device Disposal

Used crimpers may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 7,530,253 and corresponding foreign patents. Additional patents are pending.

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